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WO 03/082263 A1

(54) Title: SULFAMIC ACIDS AS INHIBITORS OF HUMAN CYTOPLASMIC PROTEIN TYROSINE PHOSPHATASES

(57) Abstract: The present invention relates to certain substituted sulfamic acids, which exhibit inhibitory action against Human Cytoplasmic Protein Tyrosine Phosphatases (HC-PTPs, Low Molecular Weight Protein Tyrosine Phosphatases, Orthophosphoric Monoester Phosphohydrolase; EC: 3.1.3.2). These compounds are indicated in the treatment or management of wounds and diseased tissues by acceleration of wound repair. The present invention also includes within its scope methods for the treatment of wounds by the administration of the aforesaid sulfamic acids as well as pharmaceutical compositions thereof. This invention relates to active pharmaceutical compositions that facilitate the healing of wounds and repair of tissue, and methods of making and using them. These pharmaceutical compositions, which are sulfamic acids and related compounds, inhibit Human Cytoplasmic Protein Tyrosine Phosphatases, an enzyme that impedes angiogenesis.

SULFAMIC ACIDS AS INHIBITORS OF HUMAN CYTOPLASMIC PROTEIN TYROSINE PHOSPHATASES

FIELD OF THE INVENTION

[0001] The invention relates generally to wound healing and tissue repair and mroe specifically to substituted sulfamic acids, which exhibit inhibitory action against Human Cytoplasmic Protein Tyrosine Phosphatases (HC-PTPs, Low Molecular Weight Protein Tyrosine Phosphatases, Orthophosphoric Monoester Phosphohydrolase; EC: 3.1.3.2).

BACKGROUND

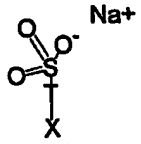
[0002] Protein tyrosine phosphatases play fundamental roles in basic cellular processes, biological signaling pathways and the pathogenesis of disease. Human Cytoplasmic Protein Tyrosine Phosphatase, also known as Low Molecular Weight Protein Tyrosine Phosphatase ("HC-PTP") is a cytoplasmic enzyme found to be a negative regulator of signaling pathways involved in angiogenesis and other processes essential to wound healing and tissue repair. HC-PTP interacts with two growth factor receptors that are essential to such healing and repair: Vascular Endothelial Growth Factor Receptor 2 ("VEGF-R2") and Platelet – Derived Growth Factor Receptor 2 ("PDGF-R2"). VEGF-R2 mediates survival, mitogenesis and migration of endothelial cells, necessary to wound healing and tissue repair. Similarly, PDGF-R2 mediates mitogenic signaling of fibroblasts as well as endothelial cells. HC-PTP dephosphorylates tyrosine residues within the cytoplasmic domain regions of VEGF-R2 and PDGF-R2, thus acting as a negative regulator of these signaling pathways. HC-PTP is further suspected to interact with and possibly impede TIE-2, an endothelial-specific receptor tyrosine kinase that provides signaling via a different pathway than VEGF-R2, and that is necessary for maintenance and expansion of primitive capillary networks and therefore essential for angiogenesis. Overexpression of HC-PTP in NIH3T3 fibroblasts results in a decrease in growth factor receptor phosphorylation and cell proliferation mediated by PDGF. A thorough discussion of these signaling mechanisms is provided in "HCPTPA, a Protein Tyrosine Phosphatase That Regulates Vascular Endothelial Growth Factor Receptor-Mediated Signal Transduction and Biological Activity," J. Biol. Chem. Vol. 274, No. 53 (12/31/1999), pp. 38183 – 38188, the entirety of

which is incorporated by reference . See also the following four articles, , the entireties of which are incorporated by reference: (1) "PDGF and TGF-beta Act Synergistically to Improve Wound Healing in the Genetically Diabetic Mouse," Brown, Rebeccah et al, J.Surg. Res. 56, pp. 562-570 (1994); (2) "Sequencing, Cloning and Expression of Human Red Cell-type Acid Phosphatase, a Cytoplasmic Phosphotyrosyl Protein Phosphatase," Wo et al, J.Biol.Chem. Vol. 267, No. 15 (May 25, 1992), pp. 10856-10865; (3) "The Three Dimensional Structure, Chemical Mechanism and Function of the Low Molecular Weight Protein Tyrosine Phosphatases," Zhang, M. et al, Adv.Prot.Phos. 9 (1995) pp. 1-23; and (4) "PDGF Receptor As A Specific *In Vivo* Target For Low Molecular Weight Phosphotyrosine Protein Phosphatase,"Chiarugi, P. et al, FEBS Letters, issue 372 (1995) pp. 49-53.

[0003] We now describe a new group of compounds, which are inhibitors of Human Cytoplasmic Protein Tyrosine Phosphatase (HC-PTP).

SUMMARY OF THE INVENTION

[0004] We have discovered that sulfamic acids, of general formula **I**, where X is either substituted or unsubstituted aryl or alkyl, particularly those identified below, in the form of free acids or pharmaceutically – acceptable pro-drugs, metabolites, analogues, derivatives, solvates or salts, inhibit HC-PTP enzyme activity. This inhibition accelerates wound healing and tissue repair (including but not limited to the treatment of peripheral and coronary vascular disease).



Where T = NH or NHNH

I

[0005] Analogues of these compounds that can be used include aryl or alkyl sulfamic acids in which the aryl group is a phenyl group that is either unsubstituted or substituted at the para and/or meta position(s) by substituents such as morpholino, or substituted piperazino group attached through its nitrogen. Analogues also include but are not limited to compounds in which the phenyl group is substituted at the position that is para to the

sulfamic acid group and/or at either or both of the positions that are meta to the sulfamic acid group, by substituents such as a halogen (F, Cl, Br, I), -OH, NO_2, or linear or branched C_{1-6} alkyl or alkenyl groups among others. Further included are pharmaceutically – acceptable pro-drugs, metabolites, analogues, derivatives, solvates or salts of these compounds. For example, sodium salts, and esters such as ethyl can be used. Such salts, esters and the like may increase hydrophobicity compared to the free acid compounds and accordingly their passage through cellular membranes may be facilitated.

Definitions

[0006] As used herein, the term "attached" signifies a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art.

[0007] The terms "halogen" or "halo" include fluorine, chlorine, bromine, and iodine.

[0008] The term "alkyl" includes C_1-C_{16} straight chain saturated, C_1-C_{16} branched saturated, C_3-C_8 cyclic saturated and C_1-C_{16} straight chain or branched saturated aliphatic hydrocarbon groups substituted with C_3-C_8 cyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, this definition shall include but is not limited to methyl (Me), ethyl (Et), propyl (Pr), butyl (Bu), pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, isopropyl (i-Pr), isobutyl (i-Bu), *tert*-butyl (*t*-Bu), *sec*-butyl (*s*-Bu), isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropylmethyl, and the like.

[0009] The term "alkenyl" includes C_2-C_{16} straight chain unsaturated, C_2-C_{11} branched unsaturated, C_5-C_8 unsaturated cyclic, and C_2-C_{16} straight chain or branched unsaturated aliphatic hydrocarbon groups substituted with C_3-C_8 cyclic saturated and unsaturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Double bonds may occur in any stable point along the chain and the carbon-carbon double bonds may have either the cis or trans configuration. For example, this definition shall include but is not limited to ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, 1,5-octadienyl, 1,4,7-nonatrienyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, ethylcyclohexenyl, butenylcyclopentyl, 1-pentenyl-3-cyclohexenyl, and the like.

[0010] The term "alkyloxy" (e.g. methoxy, ethoxy, propyloxy, allyloxy, cyclohexyloxy) represents an alkyl group as defined above having the indicated number of carbon atoms attached through an oxygen bridge.

[0011] The term "alkylthio" (e.g. methylthio, ethylthio, propylthio, cyclohexylthio and the like) represents an alkyl group as defined above having the indicated number of carbon atoms attached through a sulfur bridge.

[0012] The term "alkylamino" represents one or two alkyl groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The two alkyl groups maybe taken together with the nitrogen to which they are attached forming a cyclic system containing 3 to 8 carbon atoms with or without one C_1-C_{16}alkyl, arylC_0-C_{16}alkyl, or C_0-C_{16}alkylaryl substituent.

[0013] The term "alkylaminoalkyl" represents an alkylamino group attached through an alkyl group as defined above having the indicated number of carbon atoms.

[0014] The term "alkyloxy(alkyl)amino" (e.g. methoxy(methyl)amine, ethoxy(propyl)amine) represents an alkyloxy group as defined above attached through an amino group, the amino group itself having an alkyl substituent.

[0015] The term "alkylcarbonyl" (e.g. cyclooctylcarbonyl, pentylcarbonyl, 3-hexylcarbonyl) represents an alkyl group as defined above having the indicated number of carbon atoms attached through a carbonyl group.

[0016] The term "alkylcarboxy" (e.g. heptylcarboxy, cyclopropylcarboxy, 3-pentenylcarboxy) represents an alkylcarbonyl group as defined above wherein the carbonyl is in turn attached through an oxygen.

[0017] The term "alkylcarboxyalkyl" represents an alkylcarboxy group attached through an alkyl group as defined above having the indicated number of carbon atoms.

[0018] The term "alkylcarbonylamino" (e.g. hexylcarbonylamino, cyclopentylcarbonyl-aminomethyl, methylcarbonylaminophenyl) represents an alkylcarbonyl group as defined

above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group. The nitrogen group may itself be substituted with an alkyl or aryl group.

[0019] The term "aryl" represents an unsubstituted, mono-, di- or trisubstituted monocyclic, polycyclic, biaryl and heterocyclic aromatic groups covalently attached at any ring position capable of forming a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art (e.g. 3-indolyl, 4-imidazolyl). The aryl substituents are independently selected from the group consisting of halo, nitro, cyano, trihalomethyl, C_{1-16}alkyl, arylC_{1-16}alkyl, C_{0-16}alkyloxyC_{0-16}alkyl, arylC_{0-16}alkyloxyC_{0-16}alkyl, C_{0-16}alkylthioC_{0-16}alkyl, arylC_{0-16}alkylthioC_{0-16}alkyl, C_{0-16}alkylaminoC_{0-16}alkyl, arylC_{0-16}alkylaminoC_{0-16}alkyl, di(arylC_{1-16}alkyl)aminoC_{0-16}alkyl, C_{1-16}alkylcarbonylC_{0-16}alkyl, arylC_{1-16}alkylcarbonylC_{0-16}alkyl, C_{1-16}alkylcarboxyC_{0-16}alkyl, arylC_{1-16}alkylcarboxyC_{0-16}alkyl, C_{1-16}alkylcarbonylaminoC_{0-16}alkyl, arylC_{1-16}alkylcarbonylaminoC_{0-16}alkyl, $-C_{0-16}$alkylCOOR$_1$, $-C_{0-16}$alkylCONR$_2$R$_3$ wherein R_1, R_2 and R_3 are independently selected from hydrogen, C_1-C_{11}alkyl, arylC_0-C_{11}alkyl, or R_2 and R_3 are taken together with the nitrogen to which they are attached forming a cyclic system containing 3 to 8 carbon atoms with or without one C_1-C_{16}alkyl, arylC_0-C_{16}alkyl, or C_0-C_{16}alkylaryl substituent.

[0020] The definition of aryl includes but is not limited to phenyl, biphenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, indenyl, indanyl, azulenyl, anthryl, phenanthryl, fluorenyl, pyrenyl, thienyl, benzothienyl, isobenzothienyl, 2,3-dihydrobenzothienyl, furyl, pyranyl, benzofuranyl, isobenzofuranyl, 2,3-dihydrobenzofuranyl, pyrrolyl, indolyl, isoindolyl, indolizinyl, indazolyl, imidazolyl, benzimidazolyl, pyridyl, pyrazinyl, pyradazinyl, pyrimidinyl, triazinyl, quinolyl, isoquinolyl, 4H-quinolizinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromanyl, benzodioxolyl, piperonyl, purinyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, benzthiazolyl, oxazolyl, isoxazolyl, benzoxazolyl, oxadiazolyl, thiadiazolyl.

[0021] The term "arylalkyl" (e.g. (4-hydroxyphenyl)ethyl, (2-aminonaphthyl)hexyl, pyridylcyclopentyl) represents an aryl group as defined above attached through an alkyl group as defined above having the indicated number of carbon atoms.

[0022] The term "carbonyloxy" represents a carbonyl group attached through an oxygen bridge.

[0023] In the above definitions, the terms "alkyl" and "alkenyl" may be used interchangeably in so far as a stable chemical entity is formed, as obvious to those skilled in the art.

[0024] The compounds of the present invention also include racemic mixtures, stereoisomers and mixtures of said compounds, including isotopically-labeled and radio-labeled compounds (Goding; *Monoclonal Antibodies Principles and Practice*; Academic Press, p.104 (1986)). Such isomers can be isolated by standard resolution techniques, including fractional crystallization and chiral chromatography (Eliel, E. L. and Wilen S.H.; *Stereochemistry in Organic Compounds; John Wiley & Sons, New York*, (1993)).

[0025] The term "therapeutically effective amount" shall mean that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] Figure 1 shows compounds of the formulas 1-10.

[0027] Figure 2 shows compounds of the formulas 11-20.

[0028] Figure 3 shows compounds of the formulas 21-30.

[0029] Figure 4 shows compounds of the formulas 31-40.

[0030] Figure 5 shows compounds of the formulas 41-50.

[0031] Figure 6 shows compounds of the formulas 51-60.

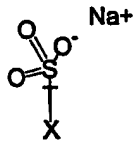
[0032] Figure 7 shows compounds of the formulas 61-70.

[0033] Figure 8 shows compounds of the formulas 71-76.

DETAILED DESCRIPTION OF THE INVENTION

[0034] We have discovered that sulfamic acids, in the form of free acids or pharmaceutically acceptable salts, inhibit HC-PTP enzyme activity. This inhibition accelerates wound healing and tissue repair.

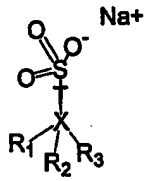
[0035] The present invention relates to compounds having the following general structural formula I, where T is equal to NH or NHNH and X is substituted or unsubstituted aryl or alkyl:



Where T = NH or NHNH

I

[0036] A preferred embodiment is when 'X' is equal to aryl as illustrated in general formula II where aryl can be selected from meta and/or para, mono, di or tri, substituted or unsubstituted phenyl, pyridyl, pyrimidyl, or mono, di or tri-substituted or unsubstituted indanyl, indolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, or 9*H*-carbazole where the substituents, R_1, R_2 and R_3, may be attached directly to the aryl group or attached via an amido (-CONH-R_4 or –NHCO-R_4), thioamido (-CSNH-R_4 or –NHCS-R_4), carboxyl (-CO_2-R_4), carbonyl (-CO-R_4), urea (-NHCONH-R_4), thiourea (-NHCSNH-R_4), sulfonamido, (-$NHSO_2$-R_4 or -SO_2NH-R_4), ether (-O-R_4), sulfonyl (-SO_2-R_4), or sulfoxyl (-SO-R_4) linking moiety as will be apparent to those skilled in the art. R_1, R_2 and R_3 may be independently selected from those listed in section 'a' below:

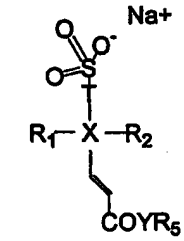


T = NH or NHNH

II

a) hydrogen, carbonyl, halo, hydroxy, nitro, trihalomethyl, cyano, branched and unbranched C_{1-8} alkyl, C_{1-8} alkylaryl, C_{3-8} cycloalkyl, fused C_{3-8} cycloalkyl, C_{0-8}alkyloxyC_{1-6}alkyl, C_{0-8}alkylcarboxyC_{1-6}alkyl, C_{0-6} alkyloxyC_{0-3} alkylaryl, methylenedioxy (e.g. a benzo[1,3]dioxole moiety), or R_4, where R_4 can be selected from i) below;

i) substituted or unsubstituted C_{1-8} alkyl, C_{0-6} alkylaryl, C_{1-6} alkyloxyC_{1-3} alkyl, C_{0-6} alkylcarboxyC_{1-6} alkyl, C_{0-6} alkyloxyC_{0-3} alkylaryl where aryl is selected from but not limited to phenyl, isoxazolyl, pyrazolyl, imidazolyl, thiazolyl, pyridyl, pyrimidyl or benzthiazolyl, where the substituents may be selected from C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-3} alkyl, halo, hydroxy, nitro, trihalomethyl, or cyano, or are selected from section 'a' above and the pharmaceutically acceptable salts or esters thereof;

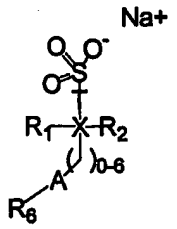


T = NH or NHNH
Y = N or O

III

[0037] A second preferred embodiment is when 'X' is equal to aryl as illustrated in general formula III where aryl can be selected from meta and/or para, mono, di or tri, substituted or unsubstituted phenyl, pyridyl, pyrimidyl, or mono, di or tri-substituted or unsubstituted indanyl, indolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, or 9*H*-carbazole where the substituents, R_1, R_2, may be attached directly to the aryl group or may be attached as will be apparent to those skilled in the art via an amido (-CONH-R_{1or2} or –NHCO- R_{1or2}), thioamido (-CSNH- R_{1or2} or –NHCS- R_{1or2}), carboxyl (-CO_2- R_{1or2}), carbonyl (-CO- R_{1or2}), urea (-NHCONH- R_{1or2}), thiourea (-NHCSNH- R_{1or2}), sulfonamido, (-$NHSO_2$- R_{1or2} or -SO_2NH-R_{1or2}), ether (-O- R_{1or2}), sulfonyl (-SO_2- R_{1or2}), or sulfoxyl (-SO- R_{1or2}) linking moiety, and may be independently selected from section 'a' above and R_5 is selected from section 'b' below:

b) substituted or unsubstituted C_{1-6} alkyl, or C_{0-6} alkylaryl, where aryl can be mono, di or tri substituted or unsubstituted biphenyl, phenyl, indolyl, pyridyl, pyrimidyl, indanyl, indolyl, benzthiazole, thiazolyl, imidazolyl, oxazolyl, isoxazolyl and the substituents are as listed in section 'a' above and the pharmaceutically acceptable salts or esters thereof;



T = NH or NHNH

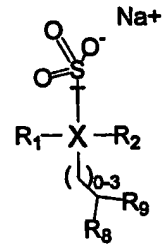
IV

[0038] A third preferred embodiment is when X is equal to aryl as illustrated in general formula IV where aryl can be selected from meta and/or para, mono, di or tri, substituted or unsubstituted phenyl, pyridyl, pyrimidyl, or mono, di or tri-substituted or unsubstituted indanyl, indolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, or 9*H*-carbazole where the substituents, R_1, R_2, may be attached directly to the aryl group or may be attached as will be apparent to those skilled in the art via an amido (-CONH-R_{1or2} or –NHCO- R_{1or2}), thioamido (-CSNH- R_{1or2} or –NHCS- R_{1or2}), carboxyl (-CO_2- R_{1or2}), carbonyl (-CO- R_{1or2}), urea (-NHCONH- R_{1or2}), thiourea (-NHCSNH- R_{1or2}), sulfonamido, (-$NHSO_2$- R_{1or2} or -SO_2NH-R_{1or2}), ether (-O- R_{1or2}), sulfonyl (-SO_2- R_{1or2}), or sulfoxyl (-SO- R_{1or2}) linking moiety, and may be independently selected from section 'a' above. A is selected from substituted or unsubstituted morpholino, piperidino, piperazino, pyrrolidino, prolyl, pyrrolidinonyl, hydantoinyl, diketopiperazinyl and R_6 is selected from section 'c' below:

c) hydroxy, carbonyl, branched and unbranched C_{1-8} alkyl, C_{3-8} cycloalkyl, fused C_{3-8} cycloalkyl, C_{0-8}alkyloxyC_{1-6}alkyl, C_{0-8}alkylcarboxyC_{1-6}alkyl, C_{0-6} alkyloxyC_{0-3} alkylaryl, or R_7, where R_7 may be attached directly or attached via an amido (-CONH-R_7 or –NHCO-R_7, or NCO-R_7 if bound via a ring nitrogen of 'A" e.g. in piperazine), thioamido (-CSNH-R_7 or –NHCS-R_7), carboxyl (-CO_2-R_7), carbonyl (-CO-R_7), urea (-NHCONH-R_7), thiourea (-NHCSNH-R_7), sulfonamido, (-$NHSO_2$-R_7 or -SO_2NH-R_7), ether (-O-R_7), sulfonyl (-SO_2-R_7), or sulfoxyl (-SO-

R_7) linking moiety as will be apparent to those skilled in the art, where R_7 can be selected from i) below;

i) substituted or unsubstituted C_{1-8} alkyl, C_{0-6} alkylaryl, C_{0-6} alkyloxyC_{1-3} alkyl, C_{0-6} alkylcarboxyC_{1-6} alkyl, C_{0-6} alkyloxyC_{0-3} alkylaryl where aryl is selected from but not limited to phenyl, isoxazolyl, pyrazolyl, imidazolyl, thiazolyl, furyl, thienyl, pyridyl or benzthiazolyl, where the substituents may be selected from C_{1-6} alkyl, C_{0-3} alkyloxy C_{1-6} alkyl, halo, hydroxy, nitro, trihalomethyl, or cyano, methylenedioxy (e.g. a benzo[1,3]dioxole moiety), branched and unbranched C_{1-8} alkyl, C_{3-8} cycloalkyl, or fused C_{3-8} cycloalkyl and the pharmaceutically acceptable salts or esters thereof;



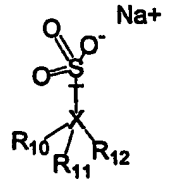
T = NH or NHNH

V

[0039] A fourth preferred embodiment is when X is equal to aryl as illustrated in general formula V where aryl can be selected from meta and/or para, mono, di or tri, substituted or unsubstituted phenyl, pyridyl, pyrimidyl, or mono, di or tri-substituted or unsubstituted indanyl, indolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, or 9*H*-carbazole where the substituents, R_1, R_2, may be attached directly to the aryl group or may be attached as will be apparent to those skilled in the art via an amido (-CONH-R_{1or2} or –NHCO- R_{1or2}), thioamido (-CSNH- R_{1or2} or –NHCS- R_{1or2}), carboxyl (-CO_2- R_{1or2}), carbonyl (-CO- R_{1or2}), urea (-NHCONH- R_{1or2}), thiourea (-NHCSNH- R_{1or2}), sulfonamido, (-$NHSO_2$- R_{1or2} or -SO_2NH-R_{1or2}), ether (-O- R_{1or2}), sulfonyl (-SO_2- R_{1or2}), or sulfoxyl (-SO- R_{1or2}) linking moiety, and may be independently selected from section 'a' above and R_8 and R_9 are independently selected from section 'd' below:

d) R_8 and R_9 may be attached directly as will be apparent to those skilled in the art, or attached via an amido (-CONH-R_{8or9} or –NHCO- R_{8or9}), thioamido (-CSNH-

R_{8or9} or –NHCS- R_{8or9}), carboxyl (-CO_2- R_{8or9}), carbonyl (-CO- R_{8or9}), urea (-NHCONH- R_{8or9}), thiourea (-NHCSNH- R_{8or9}), sulfonamido, (-$NHSO_2$- R_{8or9} or -SO_2NH- R_{8or9}), ether (-O- R_{8or9}), sulfonyl (-SO_2- R_{8or9}), or sulfoxyl (-SO- R_{8or9}) linking moiety and are selected from section a) above and the pharmaceutically acceptable salts or esters thereof.



T = NH or NHNH

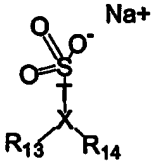
VI

[0040] A fifth preferred embodiment is when X is equal to alkyl, and can be selected from substituted or unsubstituted C_{1-6} alkyl, C_{1-6} alkyloxyC_{1-3} alkyl, C_{1-6} alkylaryl, C_{1-6} alkyloxyC_{0-3} alkylaryl, C_{3-8} cycloalkyl, piperidino, fused piperidino, C_{0-6} alkylC_{3-8}cycloalkyl, C_{0-6} alkyl morpholino, C_{0-6} alkyl piperidino, C_{0-6} alkyl piperizino, C_{0-6} alkyl pyrrolidino, where aryl can be selected from mono, di or tri, substituted or unsubstituted phenyl, pyridyl, pyrimidyl, indanyl, thienyl, furyl, indolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, where the substituents R_{10}, R_{11} and R_{12} may be independently selected from e) listed below:

e) hydrogen, halo, hydroxy, nitro, trihalomethyl, cyano, C_{0-6} alkyl carboxyC_{1-4} alkyl, C_{1-8} alkyl or the following groups which may be attached directly to the aryl group or attached via an amido, carboxyl, urea, or sulfonamido linking moiety and are selected from;

i) substituted or unsubstituted C_{1-8} alkyl, C_{0-6} alkylaryl, C_{0-6} alkyloxyC_{1-3} alkyl, methylenedioxy (e.g. a benzo[1,3]dioxole moiety), C_{0-6} alkylcarboxyC_{1-6} alkyl, C_{0-6} alkyloxyC_{0-3} alkylaryl where aryl is selected from phenyl, five or six membered heterocycles such as but not limited to isoxazolyl, pyrazolyl, imidazolyl, thiazolyl, pyridyl or benzthiazolyl, where the substituents may be selected from C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-3} alkyl, halo, hydroxy, nitro, trihalomethyl, or cyano, or the following groups which may be attached directly to the aryl ring, as will be

apparent to those skilled in the art, *via* an amido, carboxy, urea, or sulfonamido moiety and are selected from section 'a' above and the pharmaceutically acceptable salts or esters thereof.



T = NH

VII

[0041] A more preferred embodiment is illustrated by general formula VII where T is NH, and X is either phenyl, piperidinyl, piperazinyl, substituted benzthienyl, indanyl, pyridyl, cyclohexyl, 9*H*-carbazole or benzo[1,3]dioxole which is optionally substituted with substituted or unsubstituted R_{13} which is attached directly or via and amide, sulfonamide or C_{1-3} alkyl linking moiety as will be apparent to those skilled in the art, on the para-position of X with R_{13}, where R_{13} is selected from substituted piperazino, halo, hydrogen, phenyl, branched or unbranched C_{1-6} alkyl, C_{1-3} alkyl phenyl, C_{0-2} alkyl carboxyC_{1-3} alkyl ester, oxyC_{1-6}alkyl, morpholino, oxyphenyl, C_{2-6} alkenylamidoR_{15}, C_{2-6} alkenylcarboxyR_{15}, or dimethylpyrimidine,

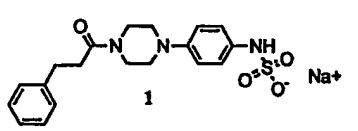
where the substituents are selected from R_{16}, where R_{16} may be attached directly or attached via an amido (-CONH- R_{16} or –NHCO- R_{16}, or NCO- R_{16} if bound via a ring nitrogen of 'A" e.g. in piperazine), sulfonamido, (-$NHSO_2$- R_{16} or -SO_2NH- R_{16}), linking moiety as will be apparent to those skilled in the art, where R_{16} can be selected from f) below;

f) substituted or unsubstituted C_{1-8} alkyl, C_{0-6} alkylaryl, C_{0-6} alkyloxyC_{1-3} alkyl, C_{0-6} alkylcarboxyC_{1-6} alkyl, C_{0-6} alkyloxyC_{0-3} alkylaryl where aryl is selected from phenyl, furyl, where the substituents may be selected from C_{1-6} alkyl, C_{0-3} alkyloxy C_{1-6} alkyl, halo, methylenedioxy (e.g. a benzo[1,3]dioxole moiety), branched and unbranched C_{1-8} alkyl, C_{3-8} cycloalkyl, or fused C_{3-8} cycloalkyl; and R_{14} is attached directly or via and amide, sulfonamide or C_{1-3} alkyl linking moiety as will be apparent to those skilled in the art, on the meta-position of X and R_{14} is selected from methoxy, bis-*meta*-methoxy, hydrogen, oxyphenyl, C_{1-3} alkyl,

oxybenzyl, and R_{15} is selected from biphenyl, methyl, ethyl, benzyl, indanyl or p-methoxybenzyl,

or when T is NH, X is C_{1-6} alkyl, which is optionally unsubstituted or substituted with phenyl, methoxy, morpholino, pyridyl, diphenyl, pyrrolidino, or thienyl, or when T= NHNH, X is methylpiperazine, or p-methoxyphenyl and the pharmaceutically acceptable salts or esters thereof.

[0042] More particularly, the present invention relates to compounds of the formulas 1-76, shown below:



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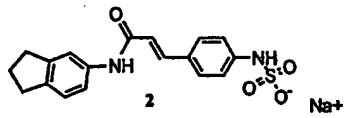

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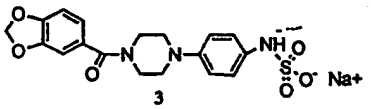

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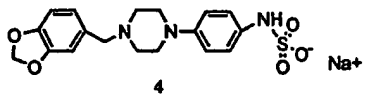

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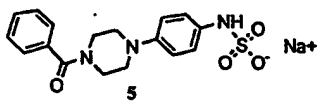

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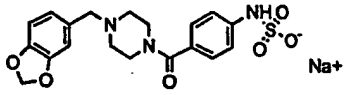

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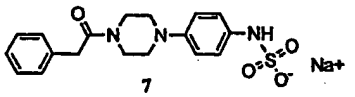

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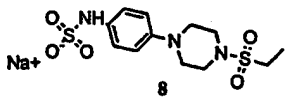

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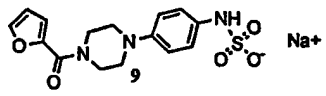

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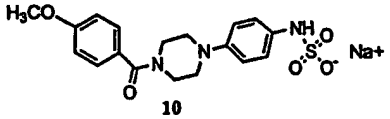

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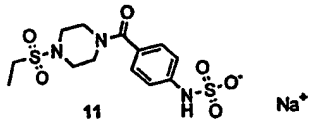

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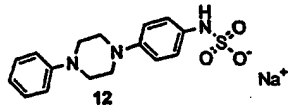

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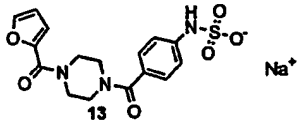

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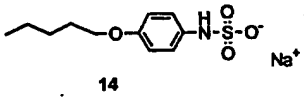

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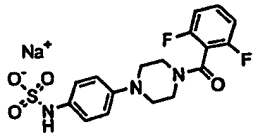

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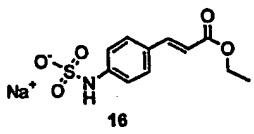

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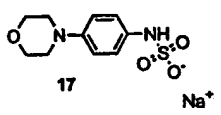

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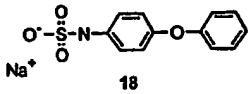

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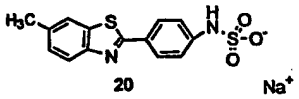

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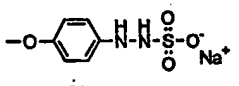

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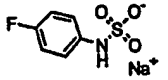

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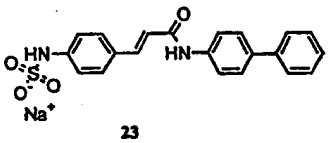

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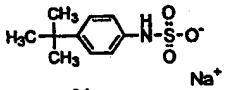

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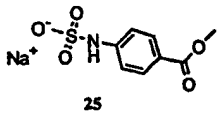

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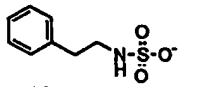

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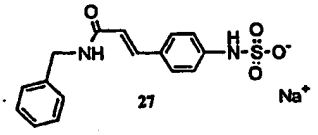

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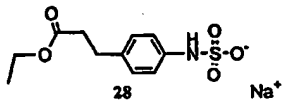

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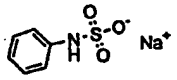

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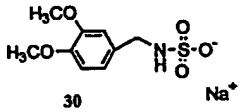

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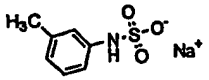

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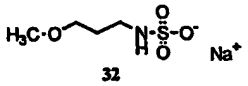

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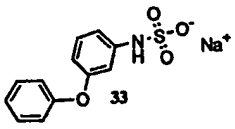

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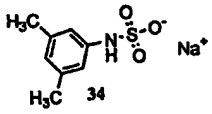

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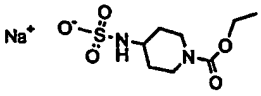

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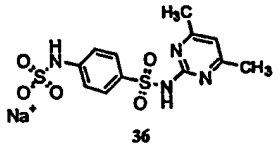

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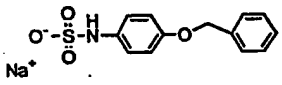

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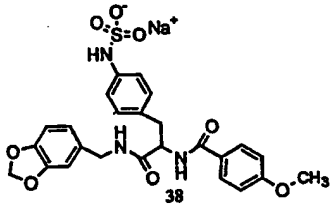

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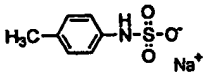

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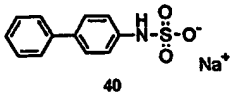

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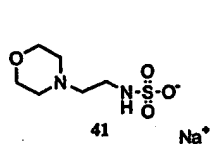
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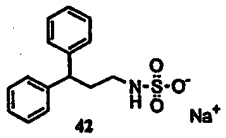
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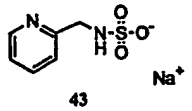
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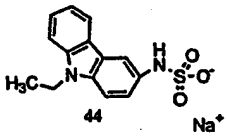
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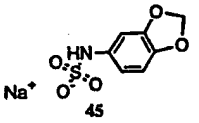
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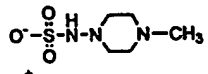
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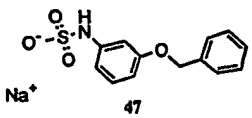
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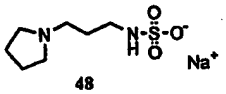
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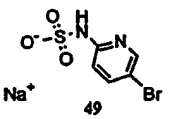
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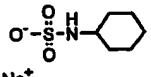
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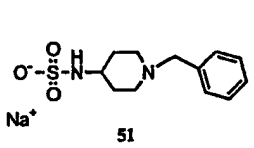

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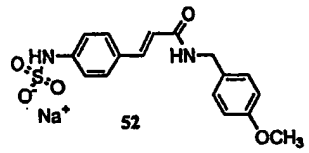

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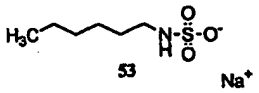

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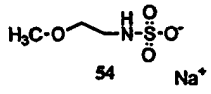

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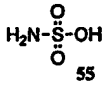

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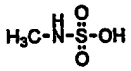

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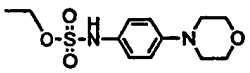

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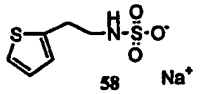

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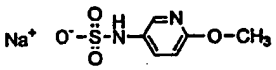

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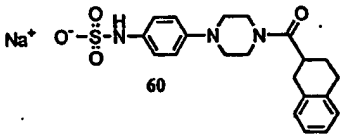

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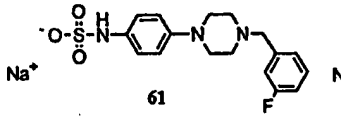
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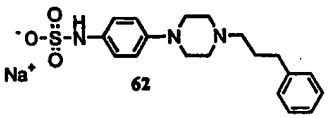
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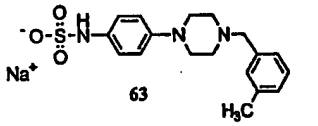
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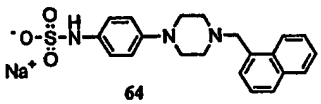
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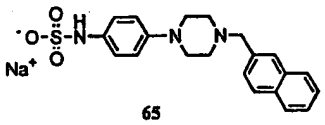
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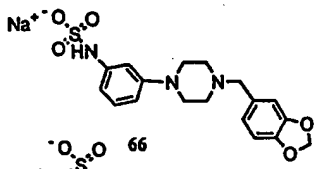
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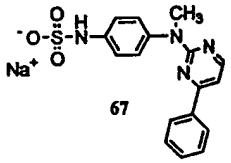
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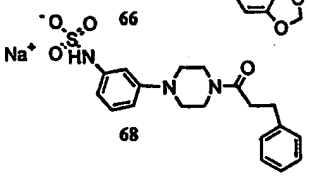
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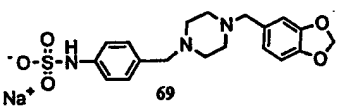
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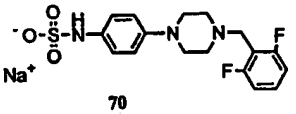
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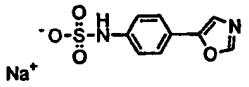
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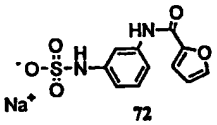
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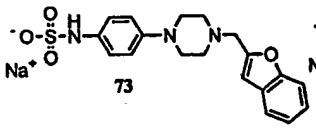
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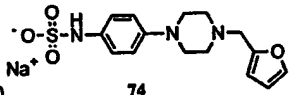
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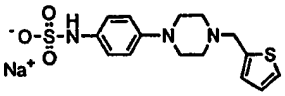
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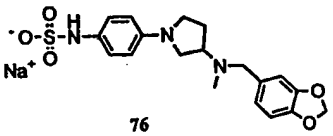

76

[0043] And the pharmaceutically acceptable salts, solvates, acids or esters thereof.

[0044] These compounds are named as follows:

Formula 1

{4-[4(3-Phenyl-propionyl)-piperazin-1-yl]-phenyl}-sulfamic acid (sodium salt)

Formula 2

{4-[2(Indan-5-ylcarbamoyl)-vinyl]-phenyl}-sulfamic acid (sodium salt)

Formula 3

{4-[4-(Benzo[1,3]dioxole-5-carbonyl)-piperazin-1-yl]-phenyl}-sulfamic acid (sodium salt)

Formula 4

[4-(4-(Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 5

[4-(4-(Benzoyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 6

[4-(4-(Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-phenyl]-sulfamic acid (sodium salt)

Formula 7

[4-(4-Phenylacetyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 8

[4-(4-Ethanesulfonyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 9

[4-(4-(Furan-2-carbonyl)-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 10

[4-(4-(4-Methoxy-benzoyl)-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 11

[4-(4-Ethanesulfonyl-piperazine-1-carbonyl)-phenyl]-sulfamic acid (sodium salt)

Formula 12

[4-(4-Phenyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 13

[4-(4-(Furan-2-carbonyl)-piperazine-1-carbonyl)-phenyl]-sulfamic acid (sodium salt)

Formula 14

(4-Pentyloxy-phenyl)-sulfamic acid

Formula 15

[4-(4-(2,6-Difluoro-benzoyl)-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 16

3-(4-Sulfoamino-phenyl) acrylic acid ethyl ester (sodium salt)

Formula 17

(4-Morpholin-4-yl-phenyl)-sulfamic acid (sodium salt)

Formula 18

(4-Phenoxy-phenyl)-sulfamic acid (sodium salt)

Formula 19

Indan-5-yl sulfamic acid (sodium salt)

Formula 20

[4-(6-Methyl-benzothiazol-2-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 21

N'(4-Methoxy-phenyl)-hydrazinesulfonic acid (sodium salt)

Formula 22

(4-Fluoro-phenyl)-sulfamic acid (sodium salt)

Formula 23

{4-[2-(Biphenyl-4-ylcarbamoyl)-vinyl]-phenyl}-sulfamic acid (sodium salt)

Formula 24

(4-*tert*-Butyl-phenyl)-sulfamic acid (sodium salt)

Formula 25

4-Sulfoamino-benzoic acid methyl ester

Formula 26

Phenethyl-sulfamic acid (sodium salt)

Formula 27

[4-(2-Benzylcarbamoyl-vinyl)-phenyl]-sulfamic acid (sodium salt)

Formula 28

3-(4-Sulfoamino-phenyl)-propionic acid ethyl ester (sodium salt)

Formula 29

Phenyl-sulfamic acid (sodium salt)

Formula 30

(3,4-Dimethoxy-benzyl)-sulfamic acid (sodium salt)

Formula 31

m-Tolyl-sulfamic acid (sodium salt)

Formula 32

(3-Methoxy-propyl)-sulfamic acid (sodium salt)

Formula 33

(3-Phenoxy-phenyl)-sulfamic acid (sodium salt)

Formula 34

(3,5-Dimethyl-phenyl)-sulfamic acid (sodium salt)

Formula 35

4-Sulfoamino-piperidine-1-carboxylic acid ethyl ester

Formula 36

[4-(4,6-Dimethyl-pyrimidin-2-ylsulfamoyl)-phenyl]-sulfamic acid (sodium salt)

Formula 37

(4-Benzyloxy-phenyl)-sulfamic acid (sodium salt)

Formula 38

{4-[2-[(Benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-2-(4-methoxy-benzoylamino)-ethyl]-phenyl}-sulfamic acid (sodium salt)

Formula 39

p-Tolyl-sulfamic acid (sodium salt)

Formula 40

Biphenyl-4-yl sulfamic acid (sodium salt)

Formula 41

(2-Morpholin-4-yl-ethyl)-sulfamic acid (sodium salt)

Formula 42

(3,3-Diphenyl-propyl)-sulfamic acid (sodium salt)

Formula 43

Pyridin-2-ylmethyl-sulfamic acid (sodium salt)

Formula 44

(*9*-Ethyl-*9H*-carbazol-3-yl)-sulfamic acid (sodium salt)

Formula 45

Benzo[1,3]dioxol-5-yl-sulfamic acid (sodium salt)

Formula 46

(*4*-Methyl-piperazin-1-yl)-sulfamic acid (sodium salt)

Formula 47

(3-Benyzloxyphenyl)-sulfamic acid (sodium salt)

Formula 48

(3-Pyrrolidin-1-yl-propyl)-sulfamic acid (sodium salt)

Formula 49

(5-Bromo-pyridin-2-yl)-sulfamic acid (sodium salt)

Formula 50

Cyclohexyl-sulfamic acid (sodium salt)

Formula 51

(1-Benzyl-piperidin-4-yl)-sulfamic acid (sodium salt)

Formula 52

{4-[2-(4-Methoxy-benzylcarbamoyl)-vinyl]-phenyl}-sulfamic acid (sodium salt)

Formula 53

Hexyl-sulfamic acid (sodium salt)

Formula 54

(2-Methoxy-ethyl)-sulfamic acid (sodium salt)

Formula 55

Sulfamic acid

Formula 56

Methyl-sulfamic acid

Formual 57

(4-Morpholin-4-yl-phenyl)-sulfamic acid ethyl ester

Formula 58

(2-Thiophen-2-yl-ethyl)-sulfamic acid

Formula 59

(6-Methoxy-pyridin-3-yl)-sulfamic acid

Formula 60

{4-[4-(1,2,3,4-Tetrahydro-naphthalene-2-carbonyl)-piperazin-1-yl]-phenyl}-sulfamic acid (sodium salt)

Formula 61

{4-[4-(3-Flouro-benzyl)-piperazin-1-yl]-phenyl}-sulfamic acid (sodium salt)

Formula 62

{4-[4-(3-Phenyl-propyl)-piperazin-1-yl]-phenyl}-sulfamic acid (sodium salt)

Formula 63

{4-[4-(3-Methyl-benzyl)-piperazin-1-yl]-phenyl}-sulfamic acid (sodium salt)

Formula 64

[4-(4-Naphthalen-1-ylmethyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 65

[4-(4-Naphthalen-2-ylmethyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 66

[3-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 67

{4-[Methyl-(4-phenyl-pyrimidin-2-yl)-amino]-phenyl}-sulfamic acid (sodium salt)

Formula 68

[3-(4-(3-Phenyl-propionyl)-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 69

[4-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-phenyl]-sulfamic acid (sodium salt)

Formula 70

{4-[4-(2,6-Diflouro-benzyl)-piperazin-1-yl]-phenyl}-sulfamic acid (sodium salt)

Formula 71

(4-Oxazol-5-yl-phenyl)-sulfamic acid (sodium salt)

Formula 72

{3-[(Furan-2-carbonyl)amino]-phenyl}-sulfamic acid (sodium salt)

Formula 73

[4-(4-Benzofuran-2-ylmethyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 74

[4-(4-Furan-2-ylmethyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 75

[4-(4-Thiophen-2-ylmethyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Formula 76

{4-[3-(Benzo[1,3]dioxol-5-ylmethyl-methyl-amino)-pyrrolidin-1-yl]-phenyl}-sulfamic acid (sodium salt)

[0045] The compounds of the present invention may have asymmetric centers and may occur as racemates, racemic mixtures, and as individual enantiomers or diastereoisomers, with all isomeric forms being included in the present invention as well as mixtures thereof.

[0046] Pharmaceutically acceptable salts of the compounds above, where a basic or acidic group is present in the structure, are also included within the scope of this invention. When an acidic substituent is present, such as $-NHSO_3H$, COOH and $P(O)(OH)_2$, there can be formed the ammonium, sodium, potassium, calcium salt, and the like, for use as the dosage form. Basic groups, such as amino or basic heteroaryl radicals, or pyridyl and acidic salts, such as hydrochloride, hydrobromide, acetate, maleate, palmoate, methanesulfonate, p-toluenesulfonate, and the like, can be used as the dosage form.

[0047] Also, in the case of the R-NH-SO_2OH being present, pharmaceutically acceptable esters can be employed, e.g., methyl, ethyl, tert-butyl, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

[0048] In addition, some of the compounds of the instant invention may be metabolized. Such metabolites are also encompassed within the scope of the invention.

[0049] In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the invention.

[0050] The term "therapeutically effective amount" shall mean that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

Preparation of Compounds

[0051] Processes, for the preparation of compounds of the present invention, are known in the chemical arts. See, for example: 1)"Preparation And Properties of Some N-Substituted Sulfamic Acids," Audrieth L. F. et al, J. Org. Chem. 9 (1944) pp. 89-101; 2) Wiley, R. A. et al, J. Med. Chem. 26 (1983) p.1077, 3)"N-Azobactams 1. The synthesis of some 3-substituted N-azamonobactam derivatives,"Curran, W. V. et al, Journal of Antibiotics, Oct 1988, pp. 1418-1429, 4) Selective N-sulfation of glucosamine derivatives using phenyl chlorosulfate in non-aqueous solvent," Kerns, R. et al, Synthetic Communication, 26 (1996), pp2671-2680. Methods to synthesize sulfamic acid esters were adopted from "Replacement of the Phosphodiester linkage in DNA with sulfamide and 3'-N-sulfamate groups," Fettes, K. et al, Chem. Commun.,(2000), pp. 765-766.

[0052] References in the literature of sulfamates include "Preparation of 2-arylbenzoxozaole and 2-arylbenzthiazole anticancer agents", Stevens et. al., PCT Int. Appl. (1996), WO 9626932, US 6034246, JP 11501024, and "Antitumor Benzothiazoles. Part 15: The synthesis and Physico-Chemical Properties of 2-(4-Aminophenyl)benzothiazole

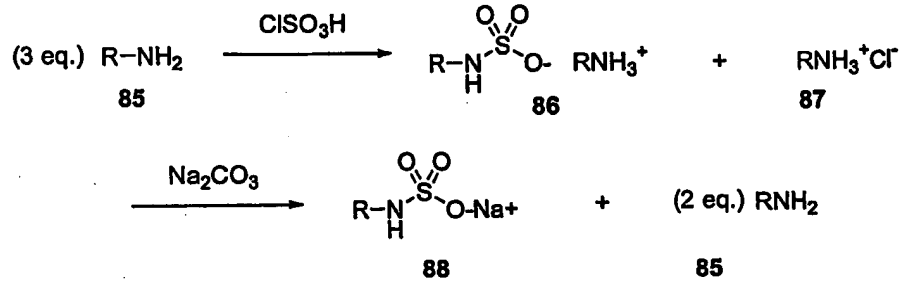
Sulfamate Salt Derivatives", Shi et. al., Bioorg. Med. Chem. Lett., (2001) 11(8), pp. 1093-1095; "Semi-quantitative and quantitative structure-taste relationships for carbo- and hetero-sulfamate (RNHSO3-) Sweeteners", Spillane et. al. J. Chem. Soc., Perkin Trans. 2 (1989), (7), pp. 741-6; "Quantitative Structure-Activity Relationship Studies of Sulfamates $RNHSO_3Na$: Distinction between Sweet, Sweet-Bitter, and Bitter Molecules", Drew et. al., Journal of Agriculture and Food Chemistry, (1998), 46 (8) pp. 3016-3026; "Synthesis and taste Properties of sodium monosubstituted phenyl sulfamates", Spillane et. al., Food Chemistry, (1994), 51 (4), pp. 405-11; "The taste of monosubstituted sulfamates", Spillane et. al., J. Chem. Soc., Chem. Commun., (1989), (9), pp. 545-7 and "Development of structure-taste relationships for sweet and non-sweet heterosulfamates", Spillane et. al. J. Chem. Soc., Perkin Trans. 2 (2000), (7), pp. 1369-1374. "Preparation of aryloxyacetyl piperazides and analogs as 5-HT1D receptor antagonists", Halazy et. al., PCT Int. Appl. (1996), WO 9602525, US 5789412, JP 10502920; "The photochemistry of para-substituted phenyl sulfamates – photo-Fries rearrangements", Lally et. al., J. Chem. Soc. Perkin Trans. 2, (1991), (6), pp. 803-7; "Basicity of nitrogen-sulfur(VI) compounds. Part 2. Protonation equilibriums of N-arylsulfamates using ultraviolet and nuclear magnetic resonance methods", Spillane et. al., J. Chem. Soc., Perkin Trans. 2, (1977), (9), pp.1180-4;

[0053] "Nonaromatic Sulfonamide Group as an Ideal Anchor for Potent Human Carbonic Anhydrase Inhibitors: Role of Hydrogen-Bonding Networks in Ligand Binding and Drug Design," Abbate, F. et. al., J. Med. Chem. (2002), 45, pp. 3583-3587.

[0054] The compounds of the present invention can be synthesized from the corresponding amine or aniline as illustrated in Scheme 1 or Scheme 2 below:

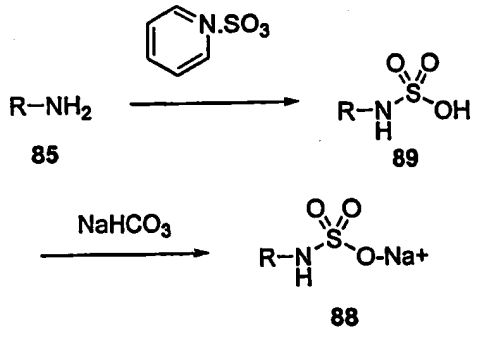
[0055] The corresponding amine in chloroform was treated with 0.33 equivalents chlorosulfonic acid (dropwise addition) at 0 °C, followed by ~2 hours at room temperature. The reaction mixture was then treated with a 0.3 M solution of Na_2CO_3 (0.3 equiv.) followed by addition of diethyl ether before concentration in vacuo. The residue was then extracted with ethanol, further concentrated then the resulting solid extracted with DMSO. This mixture was then filtered to remove solids and then diluted with water followed by lyophilization to remove DMSO to give the crude product. This product was further

purified via recrystallization to give the target sulfamic acid as it's sodium salt as illustrated in Scheme 1.



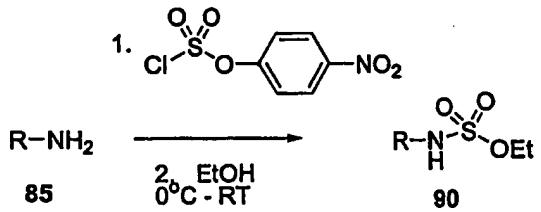
Scheme 1

[0056] Alternatively the appropriate amine (1 equiv.) in DMF is treated with solid sulfur trioxide-pyridine complex (1-3 equiv.) reaction stirred at room temperature. On completion of the reaction dry toluene was added and the solution concentrated in vacuo. The residue was treated with a solution of $NaHCO_3$ (3 equiv) and the resulting mixture sonicated for 10 minutes. The mixture was filtered and the filtrate was either concentrated in vacuo or lyophilized. The residue was extracted with boiling 95% ethanol. The ethanol extract was concentrated and the resulting solids were washed with portions of CH_2Cl_2, acetonitrile, EtOAc. The solids were collected and recrystallized from hot 95% EtOH to provide the target compounds as illustrated in Scheme 2.



Scheme 2

[0057] Sulfamic acid esters can be synthesized according to Scheme 3. The corresponding aniline is dissolved in DCM p-nitrophenylsulfonyl chloride is added in a minimum of CH_2Cl_2 and Et_3N. The reaction was stirred at room temperature for 2-5 hrs., then EtOH and Et_3N was added and the mixture was stirred for a further 12-24 hrs. Reaction mixture was washed with water and brine, concentrated and purified using prep. TLC (2X) using 2:1 EtOAc/Hex and then 2:1 Hex/EtOAc.



Scheme 3

Biological Assays

HCPTP Cloning, Expression and Purification

[0058] The full length human HCPTP gene was PCR amplified from HUVEC cDNA using the following primers:

5' Primer: 5'-CGGTCAGGATCCGCGGAACAGGCTACCAAGTCCGTG-3'
3' Primer: 5'-GGTCGACCCGGGGTACCTCAGTGGGCCTTCTCCAAGAACGC-3'

[0059] The PCR product (approximately 1 kb) was digested with Bam HI and Kpn I and ligated into the expression vector pQE30 (Qiagen) pre-digested with Bam HI and Kpn I. Clones were confirmed by DNA sequencing. One clone containing the correct sequence (S1.3) was used for all protein purifications. This clone was transformed into the bacterial strain M15 and selected on LB plates containing carbenicillin and kanamycin. The protocol for purification of human HCPTP is as follows:

[0060] 1. Inoculate 2 ml LB culture with .05 mg/ml carbenicillin and .025 mg/ml kanamycin with glycerol stock of S1.3 clone. Inoculate this starter culture into 100 ml LB culture plus carbenicillin and kanamycin and shake ovenight at 37 degrees°C.

[0061] 2. Inoculate 50 mls of overnight culture into 1 L of LB with carbenicillin and kanamycin. Shake bacterial culture until OD 600 nm ≅ .6 and induce with 1mM IPTG for 4 hours at 37°C.

[0062] 3. Lyse bacterial pellet with 25 mls of lysis buffer (50 mM sodium phosphate, pH 8.0, 300 mM NaCl, 10 mM imidazole, pH 8.0, 1mg/mL lysozyme, and 1:1000 protease inhibitor cocktail (Sigma)).

[0063] 4. Sonicate lysate (5X for 10 seconds each on ice) and spin at 10k for 20 minutes.

[0064] 5. Equilibrate Ni-NTA agarose (5 mls) with wash buffer (50 mM sodium phosphate, pH 8.0, 300 mM NaCl, and 20 mM imidazole, pH 8.0) 2X with 25 mls each. Combine lysate with Ni-NTA agarose and let bind at 4°C (rotating) for 1 hour.

[0065] 6. Wash 3X with wash buffer containing 1:1000 protease inhibitor cocktail (30 mls per wash).

[0066] 7. Elute in 15 mls of elution buffer (50 mM sodium phosphate, pH 8.0, 300 mM NaCl, 250 mM imidazole, pH 8.0, and 1:1000 protease inhibitor cocktail).

[0067] 8. Dialyze @ 4°C in 4X 1L changes of dialysis buffer [10 mM sodium acetate, 30 mM sodium phosphate ($NaH_2PO_4H_2O$), 1 mM EDTA, 60 mM sodium chloride, 1 mM DTT, pH 5.0].

[0068] 9. Add 1:1000 protease inhibitor cocktail and 20% glycerol to post-dialysis product. Store at -80°C.

Enzyme Assay

[0069] Compounds of the present invention were assayed for phosphatase (HCPTP) inhibition in a p-nitrophenylophosphate assay. The full-length human HC-PTP gene was cloned and protein purified as above. The assay buffer contained 20 millimolar sodium citrate, pH 7.0, 5 millimolar GSH, 0.5 millimolar EDTA, 0.1% BSA and 0.6 millimolar p-Nitrophenyl Phosphate. All enzyme reactions were performed in 100 microliter reaction volumes containing 40 nanograms of recombinant HCPTP protein and DMSO at a final

assay concentration of 5%. All buffer components plus compounds in DMSO were added and mixed. The reaction was started by the addition of HC-PTP enzyme. Reactions were incubated at 27 degrees Celcius and terminated with 10 microliters of 1N NaOH/MeOH, 1:1). Plates were read spectrophotometrically at 405 nanometers. See also, "Sequencing, Cloning and Expression of Human Red Cell-type Acid Phosphatase, a Cytoplasmic Phosphotyrosyl Protein Phosphatase," Wo, Y. et al, J.Biol.Chem. Vol. 267, No. 15 (May 25, 1992), p. 10858, "Enzymatic Activity of the Recombinant HCPTP's."

[0070] Compounds of the present invention demonstrated IC50 values ranging from 0.1 to 50 microlmolar where IC_{50} represents the concentration of inhibitor, which would result in 50% inhibition of HC-PTP activity.

Table 1

Compound #	HC-PTP IC_{50} micromolar	Compound #	HC-PTP IC_{50} micromolar	Compound #	HC-PTP IC_{50} micromolar
1	0.14	26	8.7	51	31
2	0.16	27	8.9	52	46
3	0.21	28	9.4	53	48
4	0.23	29	10	54	49
5	0.24	30	11	55	50
6	0.24	31	11	56	50
7	0.26	32	12	57	55
8	0.26	33	12	58	57
9	0.29	34	12	59	61
10	0.35	35	12	60	0.06
11	0.36	36	13	61	0.07
12	0.39	37	13	62	0.11
13	0.41	38	13	63	0.12
14	0.85	39	15	64	0.12
15	1.1	40	16	65	0.13
16	1.3	41	17	66	0.78
17	1.7	42	18	67	1.5
18	2.2	43	18	68	3.2
19	2.7	44	18	69	4.0
20	3.6	45	18	70	4.5
21	5.2	46	18	71	5.3
22	5.7	47	20	72	11
23	5.8	48	20	73	0.19
24	7.3	49	28	74	0.19
25	7.8	50	28	75	1.0
				76	0.07

Cell-Based Assay

[0071] Compounds of the present invention were assayed for their ability to increase PDGF-mediated cell survival in normal rat kidney fibroblasts (NRK-49F cells). In the presence of compound, HC-PTP, a negative regulator of PDGF signaling through tyrosine desphophorylation, is inhibited, thereby leading to increased cell survival.

[0072] NRK-49F (Normal Rat Kidney Fibroblast) cells were grown in DMEM + 5% FBS. Cells were then plated in DMEM containing no FBS at 500 cells/well in standard 96-well tissue culture plates. PDGF was then added at 0, 1, 5, and 10 nanograms/milliliter final assay concentration. Plates were incubated overnight at 37 degrees Celcius + 5% CO2 (Standard conditions). Compounds were added to a final assay concentration of 0, 10, 20, 30 and 50 micromolar. All wells contained a final assay concentration of 5% DMSO. Plates were incubated seven days under standard conditions and live cell number was determined by Alamar Blue fluorescence according to the manufacturers instructions (which is proportional to the number of live cells). Compounds 57 (a prodrug) and 4 demonstrated a 3-fold and 1.5-fold increase in PDGF mediated cell survival at an effective dose of approximately 10 micromolar, final assay concentration. A 1.5 – 3-fold increase of cell survival in vitro would be expected to translate to a significant response in a clinical setting i.e. an enhancement of wound healing, using compositions comprising the compounds of the invention and therapeutic methods of using the compositions of the compounds as described herein.

Wound Healing

[0073] The purpose of the following experiments was to demonstrate in vivo efficacy in models of wound healing in two different species. Compounds of the present invention were tested in an excisional wound healing models in mice and rabbits.

[0074] Briefly, groups of 5 ICR derived male mice weighing approximately 22 grams were used. During testing periods the animals were housed as one per cage. Under hexobarbital (90 milligrams per kilogram, IP) anesthesia, the shoulder and back region of each animal was shaved. A sharp punch (diameter of 12 millimeter) was used to remove the skin including the panniculus carnosus and adherent tissues. The wound area, traced onto clear

plastic sheets on days 3, 5, 7, 9 and 11, was quantitated by use of an Image analyzer. Compounds and vehicle (1.5% Carboxymethylcellulose/PBS, 20 microliters per mouse) were administered topically immediately following injury once daily for 10 consecutive days. The wound half-closure time (CT50) was determined by linear regression using Graph-Pad Prism and unpaired Student's t test was applied for comparison between treated and vehicle group at each measurement time point.

[0075] Compounds of the present invention were also tested in an excisional rabbit ear model of wound healing. Under anesthesia, full thickness ear wounds (6 mm diameter) were surgically created on ten (N=10) SPF New Zealand white female rabbits weighing 3-4 kg. In each animal, four wounds were created, and treated the same on each ear. The skin was removed to the depth of the perichondrium with a 6 millimeter biopsy punch, and perichondrium was removed by scraping the cartilage surface with a #15 scalpel blade. All wounds were treated accordingly and dressed with an occlusive dressing. All animals underwent the same surgical procedure. Compound treatments (50 microliters/wound), followed by an occlusive dressing, were applied daily. Cageside observations were performed daily. On the days 0 (intra-operative), 2, 4, 6, 8, and 10, the wounds were digitally photographed in order to assess the wound healing response to treatments, specifically wound closure over time. NIH image (1.62) analysis software was used for the area (cm^2) measurements in this evaluation. In direct comparison with the Vehicle (control) on day 10 post-operative, the results suggest wound closure significantly ($P<0.05$) increased for the following treatments; Compound **57** at 30 ug/cm^2, 10 ug/cm^2 and 3 ug/cm^2; Compound **4** at 30 ug/cm^2 and 10ug/cm^2, and Regranex at 18 ug/cm^2 (which served as a positive control).

[0076] The compounds above exhibit inhibitory activity against human cytoplasmic protein tyrosine phosphatase (HC-PTP). As discussed above, inhibition of this enzyme would logically result in, but would not be limited to the acceleration of wound healing and tissue repair. These compounds are indicated in the treatment or management of wound healing and tissue repair (including but not limited to the treatment of peripheral and coronary vascular disease).

[0077] A given compound can be used in a variety of forms, including a pharmaceutically – acceptable pro-drug, metabolite, analogue, derivative, solvate or salt.

[0078] The compounds of the present invention in the form of a free compound or a pharmaceutically – acceptable pro-drug, metabolite, analogue, derivative, solvate or salt are useful in the treatment of a mammal to accelerate healing of a wound or to mediate angiogenesis in the peripheral or coronary vascular systems, either separately or in combination with other active pharmaceutical agents. These compounds may be administered orally, topically or parenterally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein includes subcutaneous injections, aerosol, intravenous, intramuscular, intrathecal, intracranial, intrasternal injection or infusion techniques.

[0079] The present invention also has the objective of providing suitable topical, oral, and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention. The compounds of the present invention may be administered orally as tablets, aqueous or oily suspensions, lozenges, troches, powders, granules, emulsions, capsules, syrups or elixirs. The composition for oral use may contain one or more agents selected from the group of sweetening agents, flavoring agents, coloring agents and preserving agents in order to produce pharmaceutically elegant and palatable preparations. The tablets contain the acting ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be, for example, (1) inert diluents, such as calcium carbonate, lactose, calcium phosphate, carboxymethylcellulose, or sodium phosphate; (2) granulating and disintegrating agents, such as corn starch or alginic acid; (3) binding agents, such as starch, gelatin or acacia; and (4) lubricating agents, such as magnesium stearate, stearic acid or talc. These tablets may be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. Coating may also be performed using techniques described in the U.S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

[0080] A compound of the present invention, in the form of a free compound or a pharmaceutically – acceptable pro-drug, metabolite, analogue, derivative, solvate or salt, can be administered, for in vivo application, parenterally by injection or by gradual perfusion over time. Administration may be intravenously, intraperitoneally, intramuscularly, subcutaneously, intracavity, or transdermally. For in vitro studies the compounds may be added or dissolved in an appropriate biologically acceptable buffer and added to a cell or tissue.

[0081] Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, growth factors and inert gases and the like.

[0082] The present invention encompasses methods for ameliorating wound healing and for mediating tissue repair (including but not limited to treatment of peripheral and coronary vascular disease). According to these methods, a subject having a wound or in need of tissue repair, is treated at the site of the wound or damaged tissue or treated systemically, with a compound of the present invention in the form of a free compound or a pharmaceutically – acceptable pro-drug, metabolite, analogue, derivative, solvate or salt. Generally, the terms "treating", "treatment" and the like are used herein to mean affecting a subject, tissue or cell to obtain a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or disorder or sign or symptom thereof, and/or may be therapeutic in terms of a partial or complete cure for a disorder and/or adverse effect attributable to it. "Treating" as used herein covers any treatment of, or prevention of a disease or disorder in a vertebrate, a mammal, particularly a human, and includes: (a) preventing the disease or disorder from

occurring in a subject that may be predisposed to the disease or disorder, but has not yet been diagnosed as having it; (b) inhibiting the disease or disorder, i.e., arresting its development; or (c) relieving or ameliorating the disease or disorder, i.e., cause regression of the disease or disorder.

[0083] The invention includes various pharmaceutical compositions useful for ameliorating diseases and disorders, including wound healing and mediating tissue repair (including but not limited to treatment of peripheral and coronary vascular disease) and the like. The pharmaceutical compositions according to one embodiment of the invention are prepared by formulating a compound of the present invention, in the form of a free compound or a pharmaceutically – acceptable pro-drug, metabolite, analogue, derivative, solvate or salt, either alone or together with other pharmaceutical agents, suitable for administration to a subject using carriers, excipients and additives or auxiliaries. Frequently used carriers or auxiliaries include magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, milk protein, gelatin, starch, vitamins, cellulose and its derivatives, animal and vegetable oils, polyethylene glycols and solvents, such as sterile water, alcohols, glycerol and polyhydric alcohols. Intravenous vehicles include fluid and nutrient replenishers. Preservatives include antimicrobial, anti-oxidants, chelating agents and inert gases. Other pharmaceutically acceptable carriers include aqueous solutions, non-toxic excipients, including salts, preservatives, buffers and the like, as described, for instance, in Remington's Pharmaceutical Sciences, 15th ed. Easton: Mack Publishing Co., 1405-1412, 1461-1487 (1975) and The National Formulary XIV., 14th ed. Washington: American Pharmaceutical Association (1975), the contents of which are hereby incorporated by reference. The pH and exact concentration of the various components of the pharmaceutical composition are adjusted according to routine skills in the art. See Goodman and Gilman's The Pharmacological Basis for Therapeutics (7th ed.).

[0084] The pharmaceutical compositions are preferably prepared and administered in dose units. Solid dose units are tablets, capsules and suppositories. For treatment of a subject, depending on activity of the compound, manner of administration, nature and severity of the disease or disorder, age and body weight of the subject, different daily doses can be used. Under certain circumstances, however, higher or lower daily doses may be appropriate. The

administration of the daily dose can be carried out both by single administration in the form of an individual dose unit or else several smaller dose units and also by multiple administrations of subdivided doses at specific intervals.

[0085] The pharmaceutical compositions according to the invention may be administered locally or systemically in a therapeutically effective dose. Amounts effective for this use will, of course, depend on the severity of the disease or disorder and the weight and general state of the subject. Typically, dosages used in vitro may provide useful guidance in the amounts useful for in situ administration of the pharmaceutical composition, and animal models may be used to determine effective dosages for treatment of particular disorders. Various considerations are described, e.g., in Langer, Science, 249:1527, (1990); Gilman et al. (eds.) The Pharmacological Basis for Therapeutics (7th ed.) (1990), each of which is herein incorporated by reference. Dosages for parenteral administration of active pharmaceutical agents can be converted into corresponding dosages for oral administration by multiplying parenteral dosages by appropriate conversion factors. As to general applications, the parenteral dosage in mg/m^2 times 1.8 = the corresponding oral dosage in milligrams ("mg"). As to oncology applications, the parenteral dosage in mg/m^2 times 1.6 = the corresponding oral dosage in mg. An average adult weighs about 70 kg. See the Miller-Keane Encyclopedia & Dictionary of Medicine, Nursing & Allied Health, 5th Ed., (W.B. Saunders Co. 1992), pp. 1708 and 1651.

[0086] The method by which the compound of the present invention may be administered for oral use would be, for example, in a hard gelatin capsule wherein the active ingredient is mixed with an inert solid diluent, or soft gelatin capsule, wherein the active ingredient is mixed with a co-solvent mixture, such as PEG 400 containing Tween-20. A compound of the present invention may also be administered in the form of a sterile injectable aqueous or oleaginous solution or suspension. The compound of the present invention can generally be administered intravenously or as an oral dose of 0.5 to 20 mg/kg given, for example, every 3 - 12 hours.

[0087] Formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate,

calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

[0088] Aqueous suspensions normally contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspension. Such excipients may be (1) suspending agent such as sodium carboxymethyl cellulose, methyl cellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; (2) dispersing or wetting agents which may be (a) naturally occurring phosphatide such as lecithin; (b) a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate; (c) a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethylenoxycetanol; (d) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and hexitol such as polyoxyethylene sorbitol monooleate, or (e) a condensation product of ethylene oxide with a partial ester derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

[0089] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to known methods using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0090] A compound of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperature

but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

[0091] The compounds of the present invention as used in the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

[0092] For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed.

[0093] Dosage levels of the compounds of the present invention as used in the present invention are of the order of about 0.5 mg to about 20 mg per kilogram body weight, an average adult weighing 70 kilograms, with a preferred dosage range between about 5 mg to about 20 mg per kilogram body weight per day (from about 0.3 gms to about 1.2 gms per patient per day). The amount of the compound of the present invention that may be combined with the carrier materials to produce a single dosage will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain about 5 mg to 1 g of a compound of the present invention with an appropriate and convenient amount of carrier material that may vary from about 5 to 95 percent of the total composition. Dosage unit forms will generally contain between from about 5 mg to 500 mg of the present invention active ingredient.

[0094] It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

[0095] In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the invention.

[0096] In further embodiments the invention provides compositions comprising a compound of the present invention in the form of pharmaceutically – acceptable pro-drugs, metabolites, analogues, derivatives, solvates or salts, either alone or in admixture with other active pharmaceutical agents, together with a pharmaceutically acceptable diluent, adjuvant, or carrier.

[0097] While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

Experimental Synthetic Description

[0098] In order to further illustrate the practice of this invention, the following examples are included along with the general methods employed to synthesize the compounds described.

General Experimental Information

[0099] Nuclear magnetic resonance spectra (^{1}H-NMR) were measured on either a Varian (300 MHz) or a Varian (400 MHz). Chemical shifts (□) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (br.=broad, s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet), coupling constant (Hz), integration and peak assignment.

[00100] Mass spectra were measured using Atmospheric Pressure Chemical Formation (APcI) looking at positive and negative modes on a Micromass LCZ (3 KeV with a probe temperature of 400 °C and a source block at 120 °C).

[00101] LC spectra for LC/MS were measured using an eluant of CH_3CN (0.1% CF_3CO_2H)/H_2O (0.1% CF_3CO_2H) (V:V) on a Hewlett Packard HP1100 HPLC, in the range 200-300 nm with a Diode Array Detector (DAD); 5 □l per injection (Gilson 215 Autosampler) at an average concentration of 1 mg/ml; gradient: 10-100% CH_3CN in 5 minutes, 100% CH_3CN for 1 minute, 100-10% CH_3CN in 0.2 minutes, 10% CH_3CN for 1.4 minutes; LC element split 1:4 directly into ion source (500 □l/min).

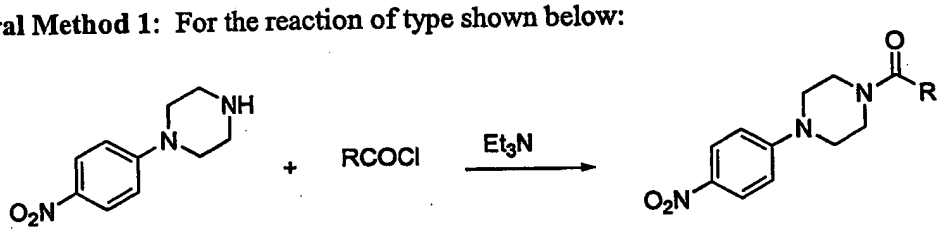
[00102] The chromatography columns used for LC in LC/MS and HPLC were 50 x 4.6 mm C-8 with 5 □m particle sizes and Zorbax 150 x 4.6 mm C-8 with 5 □m particle sizes, respectively. The same gradient was used in HPLC as in LC for LC/MS.

[00103] Reactions in solution phase were monitored by thin layer chromatography (TLC) using Merck silica gel 60F-254-coated plates (0.25 mm thickness). Flash chromatography was performed using E. Merck silica gel 60 (230-400 mesh ASTM). A Chromatotron (U.S. Patent no.4139458, Harrison Research Inc. Model 8924), preparative, centrifugally accelerated, radial, thin layer chromatography was used for difficult and/or small amounts purifications. UV 254 silica gel rotor plates (Analtech/Catalog # 02203 and 02205) were used with a thickness of 1000 or 2000 microns.

[00104] The samples were analyzed by gradient HPLC using a reverse-phase column (Zorbax Stable bond, C8, 4.6 mm x 150 mm). An injection volume of 75 uL was used for all samples. A 10 to 100% acetonitrile gradient (0.1% TFA) over 10 minutes was employed. The flowrate was set at 2.5 mL/min, and the total run time was held constant at 13.2 minutes. Signal detection was monitored by UV/VIS (254 nm and 220 nm). The purity was based on the UV peak area.

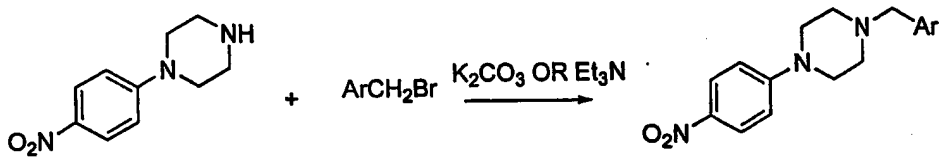
General Methods

General Method 1: For the reaction of type shown below:



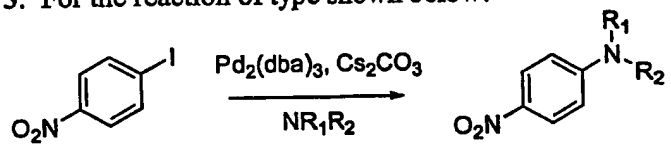
[00105] To a solution of 4-nitrophenylpiperazine (0.5 g, 2.41 mmol) in freshly-collected CH_2Cl_2 (10 mL/mmol) was added the appropriate acyl chloride (1.1 eq), triethyl amine (3 eq) and stirred at room temperature for 3 h. The reaction mixture was treated with water for 10 minutes, and the CH_2Cl_2 layer was washed with 1N HCl (twice), sat. $NaHCO_3$, and then brine (twice). The organic solution was dried (Na_2SO_4), concentrated under reduced pressure to give the desired product, which was used for the next step without purification.

General Method 2: For the reaction of type shown below:



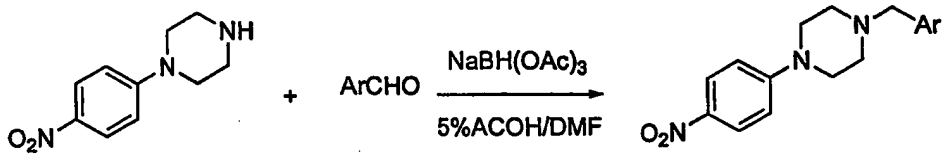
[00106] To a mixture of 4-nitrophenylpiperazine (0.5 g, 2.41 mmol) and K_2CO_3 (3 eq) in DMF (7 mL/mmol) was added appropriate benzyl bromide (1 eq) and stirred at room temperature for about 20 h. The solvent was removed under reduced pressure and diluted with CH_2Cl_2, then washed with water (twice) and brine (once). The organic solution was dried (Na_2SO_4), concentrated under reduced pressure to give the desired product, which was used for the next step without purification.

General Method 3: For the reaction of type shown below:



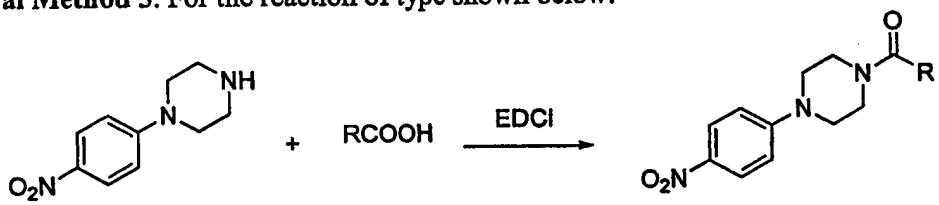
[00107] An oven-dried flask was charged with cesium carbonate (3.92 g, 12.1 mmol) that had been finely ground with a mortar and pestle under an Argon atmosphere. The flask was then charged with $Pd_2(dba)_3$ (74 mg, 1 mol%), BINAP (75 mg, 1.5 mol%) and dry toluene (20 mL). To this were added 3-iodonitrobenzene (2 g, 8.0 mmol) and 3-piperonalpiperazine (2.1 g, 9.6 mmol) and the mixture was heated to 100 °C until the starting material had been consumed as judged by TLC. The mixture was cooled to room temperature, diluted with ether, filtered, and concentrated. The crude product was purified by flash chromatography to give the desired compounds.

General Method 4: For the reaction of type shown below:



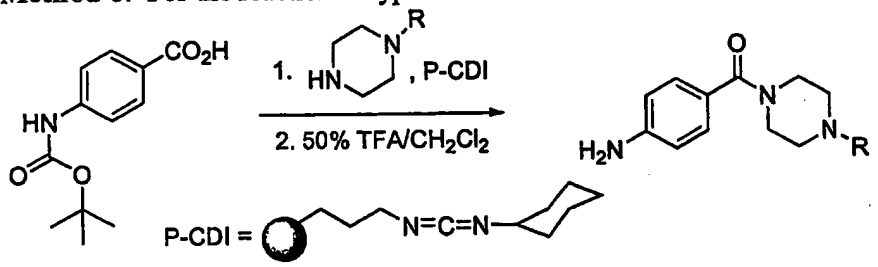
[00108] To a solution of 4-nitrophenylpiperazine (2.2 g, 11 mmol) in 5% AcOH in DMF (20 mL) was added the appropriate aldehyde (10 mmol), and the solution was stirred for 1 h at room temperature. A solution of $NaBH(OAc)_3$ (13 mmol) in 5% AcOH in DMF (5 mL) was added to the reaction mixture, and the reaction mixture was stirred for 16 h at 40 °C. The solvents was removed under high vacuum, and the residue was extracted with DCM/ aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure to give the crude product, which was purified with Silica gel column chromatography using 1% MeOH in DCM as eluent to obtain the desired product.

General Method 5: For the reaction of type shown below:



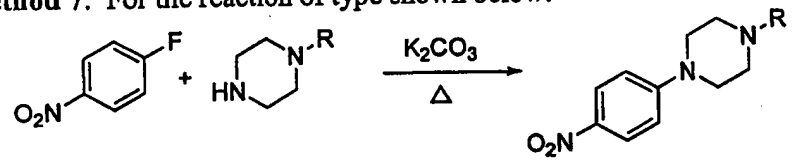
[00109] 4-Nitrophenyl piperazine (1.1 equiv) was added to a solution of EDCI (1.2 eqiv), Carboxylic acid (1.0 equiv) in dry CH_2Cl_2. The resulting mixture was stirred at room temperature for 16h. The reaction mixture was washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc/Hexanes 2:1) to give the desired 4-nitrophenyl piperazine carboxamides.

General Method 6: For the reaction of type shown below:



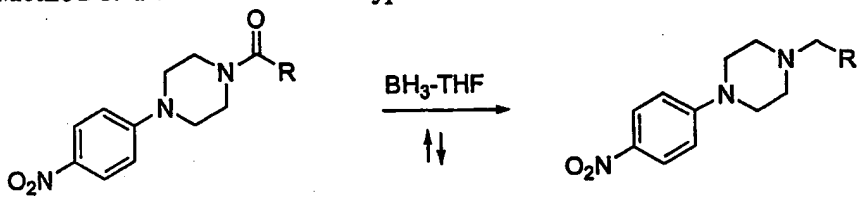
[00110] 2.5 equiv of Polymer supported carbodiimide (PS-CDI, Argonaut) was added to a solution of 4-t-BOC amino benzoic acid in dry CH_2Cl_2 (0.1M soln.). The mixture was stirred for 5 minutes and then a solution of the desired piperazine in minimum amount of CH_2Cl_2 was added, and the reaction was stirred under nitrogen for 12-16 h. Upon completion, the reaction mixture was filtered and the resin was washed with CH_2Cl_2, MeOH. The combined washings were concentrated to give the desired coupled product. This product was treated with 50% TFA/CH_2Cl_2 solution for 1h, The reaction mixture was concentrated and azeotroped with Toluene (3X). The residue was taken up in CH_2Cl_2 and washed with sat. $NaHCO_3$, water. The organics were dried and concentrated to give the desired product.

General Method 7: For the reaction of type shown below:



[00111] A suspension of 4-Fluoronitrobenzene (1.0 equiv), amine (1.2 equiv), K_2CO_3 (2 equiv.) in DMSO was heated at 900 for 12 h. The reaction mixture was diluted with water, and extracted with CH_2Cl_2. The organics were washed with water, brine, dried (Na_2SO_4) and concentrated to give crude residues that were purified by flash chromatography (SiO_2, Hexanes/EtOAc) to give the target compounds.

General Method 8: For the reaction of type shown below:



[00112] A clean dry 3-necked flask, fitted with a condensor and thermometer, was charged with the 4-nitrophenyl piperazinecarboxamide (1 equiv), and dry THF to give a 0.1M solution. 1M BH_3-THF solution (2 equiv) was slowly added to the above solution under nitrogen. The resulting solution was stirred at room temp for 45 min, and then the heated at reflux for 15h. Reaction was cooled in an ice bath and acidified with 3N HCl, the solution was warmed to room temp and refluxed for 3h. Reaction mixture was cooled to room temp and basified with 15% NaOH. Reaction mixture was diluted with EtOAc, and washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, Hexanes/EtOAc 1:2)

General Method 9: Reduction of the nitro functional group by hydrogenation in presence of Pd/C.

[00113] A mixture of nitro compound and 10% Pd-C (20% by weight) in THF/MeOH (1/1, 20 mL/mmol) was flushed with H_2 (2X), and then stirred under an atmosphere of H_2 for 2 h. The reaction mixture was filtered through Celite, washed with THF (2 X 20 mL/mmol), EtOAc (2 x 10 ml/mmol), and MeOH (2 x 20 ml/mmol) and concentrated under reduced pressure to give appropriate aniline derivatives.

General Method 10: Reduction of the nitro functional group using $SnCl_2$. $2H_2O$

[00114] A mixture of compound nitro compound and $SnCl_2$,dihydrate (8 eq) in EtOH/DMF (1/1, 10 mL/mmol) was stirred at 45 °C for about 20 h. The solvent was removed under reduced pressure and treated with saturated K_2CO_3 (pH ~ 10), then extracted with CH_2Cl_2 (3X). The organic layer was washed with $NaHCO_3$ (twice) and brine (once). The organic solution was dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography to give the desired compounds.

General Method 11: Reduction of the nitro functional group using Ra-Ni and Hydrazine hydrate.

[00115] To a solution of nitro compound (0.8 mmol) in THF/MeOH (1:2, 20 mL) was added a slurry of Raney Ni (500 mg), hydrazine monohydrate (80 mmol), and the reaction mixture was heated to 60 °C for 2 h. The slurry was filtered through a short pad of Celite, and the filtrate was concentrated. The residue was extracted with DCM/aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure to give the desired aniline product.

General Methods for preparation of sodium salts of sulfamic acids:

Method A - Compounds 2, 14,18, 19-21, 23-28, 30-37, 39-49, 51-54, 58 and 59:

[00116] A clean dry flask was flushed with nitrogen and charged with the appropriate amine (1 equiv.). Dry chloroform was added to the flask and the resulting solution (0.7 M) was cooled in an ice bath (0°C). Chlorosulfonic acid (0.33 equiv.) was slowly added to the amine solution and the resulting mixture was stirred at 0°C for additional 10 minutes. The ice bath was removed and the reaction mixture was allowed to warm to room temperature and stirred at the same for two hours. 0.3 M solution of Na_2CO_3 (0.3 equiv.) was added to the reaction and stirred for 10 mins. Ether (5ml) was added and the reaction stirred vigorously for 10 mins. Reaction was concentrated in vacuo. The residue was treated with 10 mL of ethanol and filtered. The solids were washed with additional portions of ethanol (3 x 5 mL.), dried and collected. The solids were solvated in DMSO (2-5 mL) and the solution was filtered through a cotton plug. The filtrate was diluted with water (50 mL) and lyophilized to remove DMSO. The lyophilization process was repeated as required to remove residual amount of DMSO. The lyophilized solid was recrystallized from hot 95% EtOH to provide the target compounds. The compounds were characterized by ^1H NMR and MS.

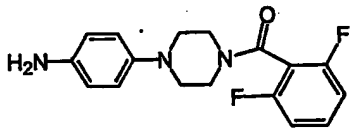
Method B – Compounds 1, 3-13, 15-17, 22, 60-76:

[00117] A clean dry flask was flushed with nitrogen and charged with the dry DMF followed by the appropriate amine (1 equiv.) Solid sulfur trioxide-pyridine complex (1-3

equiv.) was added in a single portion and the reaction was stirred at room temperature for 1-12 h. When the starting amine was completely consumed (as indicated by analytical HPLC) the reaction was quenched with either : 1) a 5 ml solution of $NaHCO_3$ (3 equiv) or 2) a slurry of Bio-Rex® 70 resin 50-100 mesh (10 equiv) in 10 ml H_2O. The resulting mixture was sonicated for 10 minutes and filtered. The filtrate was either concentrated in vacuo or lyophilized. The residue was extracted with boiling 95% ethanol. The ethanol extract was concentrated and the resulting solids were washed with portions of acetonitrile, EtOAc. The solids were collected and recrystallized from hot 95% EtOH to provide the target compounds. The compounds were characterized by ^1H NMR, HPLC and MS.

Analytical Data for representative anilines and nitro compound precursors of sulfamic acids:

Compound 91

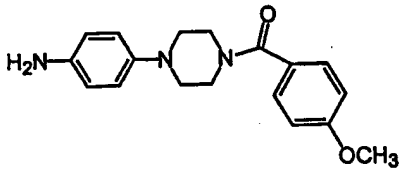


91

Compound 91 was prepared by General Method 9, by reduction of the nitro precursor which was made by general method General method 1.

Data; HPLC: retention time 2.87 min, 96% at 254 nm; ^1H NMR (400 MHz, DMSO-d_6); 2.85 (m, 2H), 2.96 (m, 2H), 3.33 (m, 2H), 3.74 (m, 2H), 5.85 (s, br, 2H, NH_2), 6.56 (d, 1H, J = 8.8), 6.72 (d, 1H, J = 8.8), 7.21 (m, 2H), 7.55 (m, 1H).

Compound 92

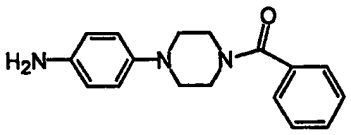


92

Compound 92 was prepared by General Method 9, by reduction of the nitro precursor which was made by general method General method 1.

Data; HPLC: retention time 2.81 min, 96% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.85 (s, br, 4H), 3.55 (s, br, 4H), 5.10 (s, br, 2H, NH_2), 6.50 (d, 1H, J = 8.8), 6.70 (d, 1H, J = 8.8), 6.96 (d, 1H, J = 8.8), 7.36 (d, 1H, J = 8.8).

Compound 93

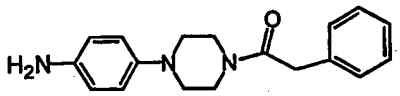


93

Compound 93 was prepared by General Method 9, by reduction of the nitro precursor which was made by general method General method 1.

Data; HPLC: retention time 2.60 min, 97% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.90 (s, br, 4H), 3.40 (s, br, 2H), 3.70 (s, br, 2H), 4.72 (s, br, 2H, NH_2), 6.47 (d, 2H, J = 8.4), 6.69 (d, 2H, J = 8.4), 7.43 (m, 5H); LC/MS: LC retention time 0.77 minutes; 282.1 (100%, $[MH]^+$) – $C_{17}H_{19}N_3O$.

Compound 94

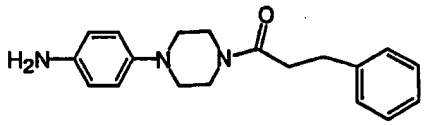


94

Compound 94 was prepared by General Method 9, by reduction of the nitro precursor which was made by general method General method 1.

Data; HPLC: retention time 2.81 min, 94% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.79 (m, 4H), 3.56 (s, br, 4H), 3.72 (s, 2H), 5.08 (s, br, 2H, NH_2), 6.50 (d, 2H, J = 8.8), 6.68 (d, 2H, J = 8.8), 7.27 (m, 5H); LC/MS: LC retention time 0.83 min; 296.1 (100%, $[MH]^+$) – $C_{18}H_{21}N_3O$.

Compound 95

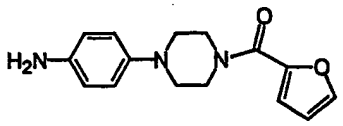


95

Compound 95 was prepared by General Method 9, by reduction of the nitro precursor which was made by general method General method 1.

Data; HPLC: retention time 3.18 min, 100% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.62 (t, 2H, J = 6.8), 2.78 (m, 6H), 3.52 (m, 4H), 4.88 (s, br, 2H, NH_2), (d, 2H, J = 8.7), 6.67 (d, 2H, J = 8.7), 7.24 (m, 5H); LC/MS: LC retention time 0.92 min; 310.1 (100%, $[MH]^+$) – $C_{19}H_{23}N_3O$.

Compound 96

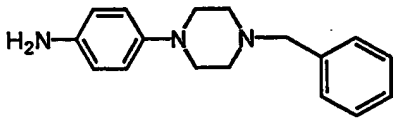


96

Compound 95 was prepared by General Method 9, by reduction of the nitro precursor which was made by general method General method 1

Data; HPLC: retention time 2.27 min, 94% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.91 (m, 4H), 3.73 (s, br, 4H), 4.64 (s, br, 2H, NH_2), 6.47 (d, 2H, J = 8.4), 6.60 (q, 1H, J = 1.6), 6.69 (d, 2H, J = 8.4), 6.98 (d, 1H, J = 3.6), 7.82 (s, 1H).

Compound 97

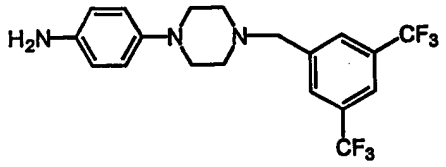


97

Compound 97 was prepared by General Method 10, by reduction of the nitro precursor which was made by general method General method 2.

Data; HPLC: retention time 1.99 min, 91% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.45 (m, 4H), 2.87 (m, 4H), 3.48 (s, 2H), 4.55 (s, br 2H, NH_2), 6.44 (d, 2H, J= 8.7), 6.63 (d, 2H, J= 8.7), 7.30 (m, 5H).

Compound 98

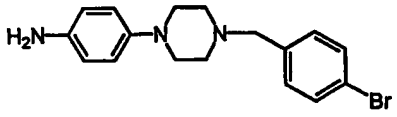


98

Compound 98 was prepared by General Method 10, by reduction of the nitro precursor which was made by general method General method 2.

Data; HPLC: retention time 4.48 min, 100% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.51 (m, 4H), 3.06 (m, 4H), 3.71 (s, 2H), 6.86 (d, 2H, J= 8.8), 7.40 (d, 2H, J= 8.8), 8.00 (m, 3H).

Compound 99

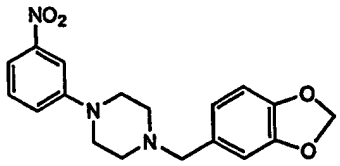


99

Compound 98 was prepared by General Method 10, by reduction of the nitro precursor which was made by general method General method 2.

Data; HPLC: retention time 2.68 min, 95% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.44 (m, 4H), 2.87 (m, 4H), 3.45 (s, 2H), 4.55 (s, br, 2H, NH_2), 6.44 (d, 2H, J= 8.4), 6.63 (d, 2H, J= 8.4), 7.25 (d, 2H, J= 8.4), 7.48 (d, 2H, J= 8.4); LC/MS: LC retention time 0.81 min; 346, 348 (100%, $[M]^+$) – $C_{17}H_{20}BrN_3$.

Compound 100

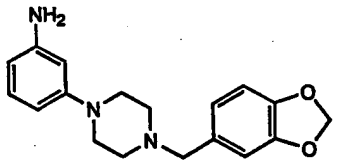


100

Compound 100 was prepared by General Method 3.

Data; ^{1}H NMR (400 MHz, $CDCl_3$); 2.58 (m, 4H), 3.27 (m, 4H), 3.47 (s, 2H), 5.94 (s, 2H), 6.76 (s, 2H), 6.87 (s, 1H), 7.18 (d, 1H), 7.35 (t, J = 8 Hz, 1H), 7.62 (m, 2H).

Compound 101

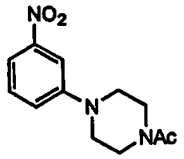


101

The corresponding aniline compound 101 was prepared by reduction of compound 100 General Method 10.

Data; HPLC: retention time 2.98min, 91% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.44 (m, 4H), 2.99 (m, 4H), 3.88 (s, 2H), 4.81 (s, br, 2H), 5.96 (s, 2H), 6.10 (m, 3H), 6.81 (m, 4H); LC/MS: LC retention time 0.73 min; 312 (100%, $[MH]^+$) – $C_{18}H_{21}N_3O_2$.

Compound 102

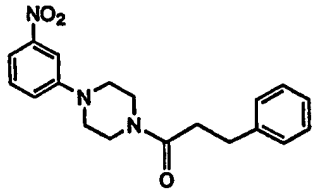


102

Compound 102 was prepared by General Method 3.

Data; ^{1}H NMR (400 MHz, $CDCl_3$); 2.15 (s, 3H), 3.29 (m, 4H), 3.64 (m, 2H), 3.79 (m, 2H), 7.20 (m, 1H), 7.39 (t, 1H), 7.71 (m, 2H).

Compound 103

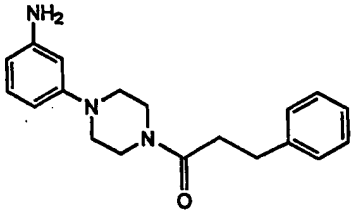


103

The above compound 103 was prepared by General Method 1.

Data; ^{1}H NMR (400 MHz, $CDCl_3$); 2.67 (t, J = 8 Hz, 2H), 2.99 (t, J = 8.4 Hz, 2H), 3.10 (m, 2H), 3.21 (m, 2H), 3.54 (m, 2H), 3.79 (m, 2H), 7.25 (m, 7H), 7.67 (m, 2H).

Compound 104

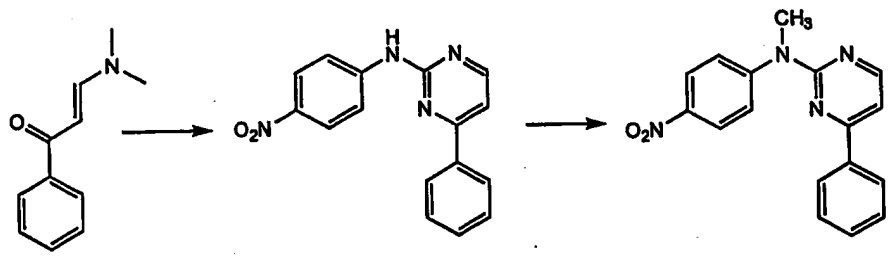


104

The above compound 104 was prepared by reduction of compound 103 by General Method 10.

Data; HPLC: retention time 3.21 min, 96% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.47 (m, 2H), 2.78 (m, 2H), 2.93 (m, 4H), 3.52 (m, 4H), 4.81 (s, br, 2H), 6.10 (m, 2H), 6.82 (t, 1H), 7.24 (m, 6H); LC/MS: LC retention time 1.00 min; 310 (100%, $[MH]^+$) – $C_{19}H_{23}N_3O$.

Compound 107

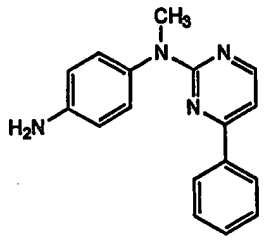


105 106 107

3-dimethylamino-1-phenyl-2-propen-1-one 105 (1.93 g, 5.7 mmol) in isopropanol (200 mL) was added 4-nitrophenylguanidine hydrochloride (2.4 h, 5.7 mmol) and sodium hydroxide (0.53 g, 6.8 mmol) and the mixture was refluxed overnight. After cooling to room temperature, the suspension was filtered and washed with isopropanol and then the residue was suspended in water, stirred for 30 min, filtered and washed with water, isopropanol, and ether. After drying under vacuum, N-(4-nitrophenyl-4-phenyl-2-pyrimidine was obtained as yellow solid 106 (1.1 g, 66%). A suspension thereof (0.6 g, 2.1mmol) in dry THF (30 mL) was treated with potassium t-butoxide (2.24 mL of 1 M solution THF, 2.3 mmol) and stirred for 10 min at room temperature, then iodomethane (1.28 mL, 21 mmol) was added and the mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was suspended in water for 20 min, filtered, washed with water, isopropanol, and ether. The collected solid was dried under vacuum to give the desired product 107 as yellow solid (0.54 g, 84%).

Compound 107 HPLC: retention time 6.43 min, 91% at 254 nm; ^{1}H NMR (400 MHz, $CDCl_3$); 3.74 (s, 3H), 7.21 (d, J = 5.6 Hz, 2H), 7.48 (m, 3H), 7.61 (d, J = 9.2 Hz, 2H), 8.0 (m, 2H), 8.25 (d, J = 9.2 Hz, 2H), 8.47 (d, J = 5.6 Hz, 1H).

Compound 108

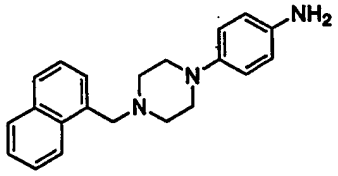


108

The above aniline compound 108 was prepared by reduction of Compound 107 General Method 9.

Data; HPLC: retention time 3.17 min, 97% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 3.41 (s, 3H), 5.0 (s, br, 2H), 6.56 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 5.2 Hz, 1H), 7.45 (m, 3H), 8.01 (m, 2H), 8.34 (d, J = 5.2 Hz, 1H).

Compound 109

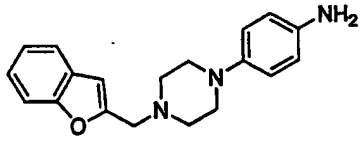


109

Compound 109 was prepared by General Method 11, by reduction of the nitro precursor which was made by general method General method 2.

Data; ^{1}H NMR (300 MHz, $CDCl_3$); 2.63 (m, 4H), 2.99 (m, 4H), 3.35 (s, br, 2H, NH_2), 3,92 (s, 2H), 6.58 (d, 2H, J = 8.7), 6.75 (d, 2H, J = 8.7), 7.34-7.83 (2H), 8.27-8.30 (1H).

Compound 110

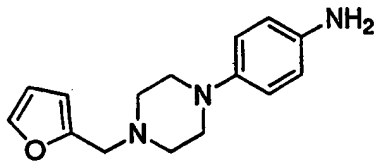


110

Compound 110 was prepared by General Method 11, by reduction of the nitro precursor which was made by general method General method 4.

Data; ^{1}H NMR (300 MHz, $CDCl_3$); 2.65 (m, 4H), 3.04 (m, 4H), 3.69 (s, 2H), 6.56 (s, 1H), 6.57 (d, 2H, J = 9.3), 6.75 (d, 2H, J = 9.3), 7.14-7.22 (2H), 7.41-7.49 (2H).

Compound 111

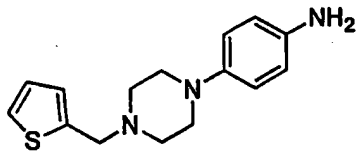


111

Compound 111 was prepared by General Method 11, by reduction of the nitro precursor which was made by general method General method 4.

Data; ^{1}H NMR (300 MHz, $CDCl_3$); 2.56 (m, 4H), 3.00 (m, 4H), 3.52 (s, 2H), 6.16 (m, 1H), 6.25 (m, 1H), 6.55 (d, 2H, J = 8.7), 6.73 (d, 2H, J = 8.7), 7.32 (m, 1H).

Compound 112

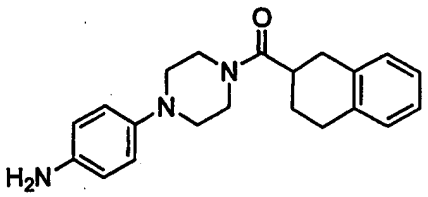


112

Compound 112 was prepared by General Method 11, by reduction of the nitro precursor which was made by general method General method 4.

Data; ^{1}H NMR (300 MHz, $CDCl_3$); 2.59 (m, 4H), 3.01 (m, 4H), 3.35 (s, br, 2H, NH_2), 3.72 (s, 2H), 6.58 (d, 2H, J = 9.0), 6.75 (d, 2H, J = 9.0), 6.88-6.90 (2H), 7.19 (m, 1H).

Compound 113

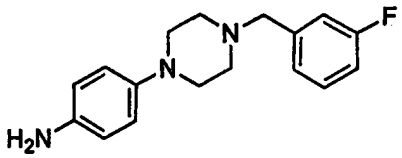


113

Compound 113 was prepared by General Method 11, by reduction of the nitro precursor which was made by general method General method 5.

Data: HPLC: retention time 3.53 min, 93% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 1.68 (m, 1H), 1.92 (m, 1H), 2.85 (m, 8H), 3.04 (m, 1H), 3.63 (m, 4H), 4.64 (s, 2H), 6.50 (d, 2H, J=8.8), 6.72 (d, 2H, J=8.8), 7.08 (s, 1H).

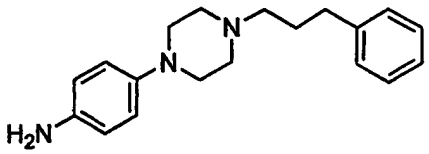
Compound 114



Compound 114 was prepared by General Method 11, by reduction of the nitro precursor which was made by general method General method 2.

Data: HPLC: retention time 1.80min, 100% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.50 (s, 4H), 2.92 (s, br, 4H), 3.54 (s, 2H), 4.58 (s, br, 2H,), 6.50 (d, 2H, J=8.4), 6.68 (d, 2H, J=8.8), 7.13 (m, 3H), 7.38 (m, 1H).

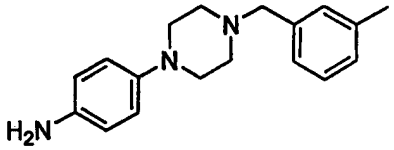
Compound 115



Compound 115 was prepared by General Method 11, by reduction of the nitro precursor which was made by general method General method 8.

Data: HPLC: retention time 2.71 min, 91% at 254 nm; ^{1}H NMR (300 MHz, DMSO-d_6); 1.78 (m, 2H), 2.34 (m, 2H), 2.50 (m, 4H), 2.64 (m, 2H), 2.95 (m, 4H), 4.60 (s, br, 2H), 6.56 (d, 2H, J=9), 6.73 (d, 2H, J=8.7), 7.25 (m, 5H).

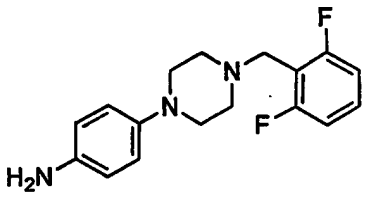
Compound 116



Compound 116 was prepared by General Method 11, by reduction of the nitro precursor which was made by general method General method 2.

Data: HPLC: retention time 2.34 min, 94% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.30 (s, 3H), 2.47 (m, 4H), 2.89 (m, 4H), 3.46 (s, 2H), 4.58 (s, br, 2H), 6.47 (d, 2H, J=8.8), 6.66 (d, 2H, J=8.8), 7.09 (m, 3H), 7.21 (m, 1H).

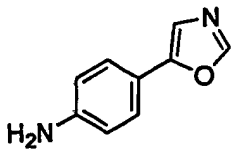
Compound 117



Compound 117 was prepared by General Method 11, by reduction of the nitro precursor which was made by general method General method 8.

Data: HPLC: retention time 1.83 min, 99% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.50 (m, 4H), 2.86 (m, 4H), 3.61 (s, 2H), 4.55 (s, br, 2H), 6.46 (d, 2H, J=8.8), 6.64 (d, 2H, J=8.8), 7.10 (m, 2H), 7.41 (m, 1H).

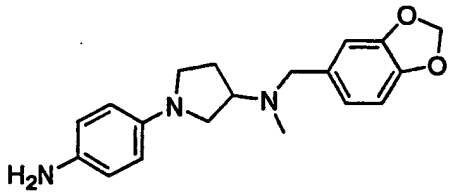
Compound 118



Compound 114 was prepared by General Method 19, by reduction of the nitro precursor.

Data: ^{1}H NMR (DMSO-d_6) 5.42 (s, 2H), 6.58 (d, 2, J = 8.43 Hz), 6.86 (d, 2H, J = 7.77 Hz), 7.26 (s, 1H), 7.39 (s, 1H).

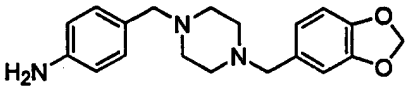
Compound 119



Compound 119 was prepared by General Method 11, by reduction of the nitro precursor which was made by general method General method 3.

Data: HPLC: retention time 2.59 min, 98% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.90 (s, br, 4H), 3.58 (s, br, 4H), 4.63 (s, br, 2H), 6.08 (s, 2H), 6.49 (d, 2H, J=8.8), 6.71 (d, 2H, J=8.8), 6.95 (m, 3H).

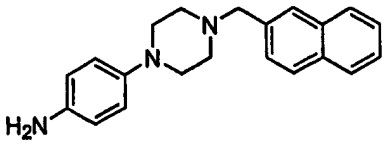
Compound 120



Compound 120 was prepared by General Method 11, by reduction of the nitro precursor which was made by general method General method 2.

Data: ^{1}H NMR (400 MHz, DMSO-d_6): 2.30 (s, br, 7H), 3.24 (s, 2H), 3.34 (s, 3H), 4.93 (s, 2H), 5.97 (s, 2H), 6.48 (d, 2H, J=8.4), 6.71 (d, 1H, J=8.8), 6.82 (m, 2H), 6.89 (d, 2H, J=8.0).

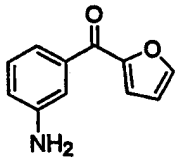
Compound 121



Compound 121 was prepared by General Method 11, by reduction of the nitro precursor which was made by general method General method 2.

Data: HPLC: retention time 2.74 min, 91% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6): 2.54 (m, 4H), 2.92 (m, 4H), 3.67 (s, 2H), 4.57 (s, br, 2H), 6.48 (d, 2H, J=8.8), 6.67 (d, 2H, J=8.8), 7.49 (m, 3H), 7.81 (s, 1H), 7.89 (m, 3H).

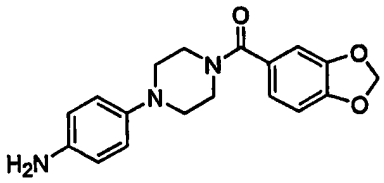
Compound 122



Compound 122 was prepared by General Method 9, by reduction of the nitro precursor which was made by general method General method 1.

Data: HPLC: retention time 1.53 min, 99% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 5.13 (brs, 2H), 6.31 (dd, 1H), 6.67-6.86 (m, 1H), 6.81 (dd, 1H), 6.94 (t, 1H), 7.06 (t, 1H), 7.31 (d, 1H), 7.90 (m, 1H), 9.83 (s, 1H),

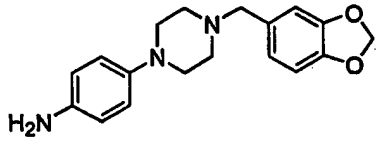
Compound 123



Compound 122 was prepared by General Method 11, by reduction of the nitro precursor which was made by general method General method 5.

Data: HPLC: retention time 2.59 min, 98% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6): 2.90 (s, 4H), 3.58(s, br, 4H), 4.63 (s, 2H), 6.08 (s, 2H), 6.49 (d, 2H, J=8.8), 6.61 (d, 2H, J=8.8), 6.95 (m, 3H).

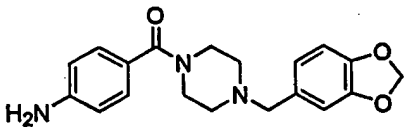
Compound 124



Compound 124 was prepared by General Method 9, by reduction of the nitro precursor which was made by general method General method 7.

Data: HPLC: retention time 1.99 min. 98% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.46 (m, 4H), 2.87 (m, 4H), 3.40 (s, 2H), 4.58 (brs, 2H), 5.98 (s, 2H), 6.47 (d, 2H, J = 8.4 Hz), 6.66 (d, 2H, J = 8.8 Hz), 6.76 (dd, 1H, J = 1.6, 8.0 Hz), 6.85 (d, 1H, J = 8.0 Hz), 6.87 (d, 1H, J = 1.6 Hz).

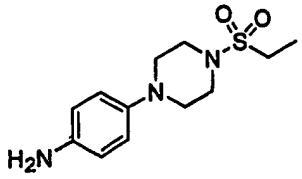
Compound 125



Compound 125 was prepared by General Method 9, by reduction of the nitro precursor which was made by general method General method 6.

Data: HPLC: retention time 2.00 min. 100% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.33 (m, 4H), 3.39 (s, 2H), 3.47 (brs, 4H), 5.51 (s, 2H), 5.99 (s, 2H), 6.53 (d, 2H, J = 8.0 Hz), 6.75 (d, 1H, J = 8.0 Hz), 6.83-6.86 (m, 2H), 7.09 (d, 2H, J = 8.4Hz).

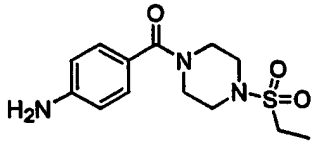
Compound 126



Compound 126 was prepared by General Method 9, by reduction of the nitro precursor which was made by general method General method 5.

^{1}H NMR (400 MHz, CD_3OD); 1.33 (t, 3H), 3.03-3.09 (m, 6H), 3.38-3.40 (m, 4H), 6.70 (d, 2H), 6.84 (d, 2H),.

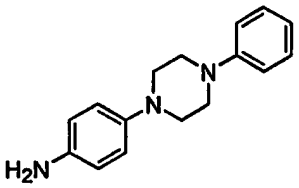
Compound 127



Compound 127 was prepared by General Method 9, by reduction of the nitro precursor which was made by general method General method 6.

^{1}H NMR (400 MHz, DMSO-d_6); 1.21 (t, 3H), 3.07 (q, 2H), 3.19 (m, 4H), 3.55 (m, 4H), 5.56 (s, 2H), 6.54 (d, 2H), 7.14 (d, 2H).

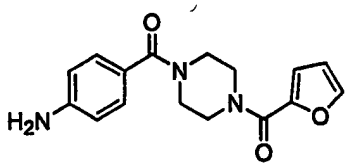
Compound 128



Compound 128 was prepared by General Method 9, by reduction of the nitro precursor which was made by general method General method 5.

Data: HPLC: retention time 2.19 min. 100% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 3.02-3.05 (m, 4H), 3.23-3.29 (m, 4H), 4.63 (brs, 2H), 6.52 (d, 2H, J = 8.8 Hz), 6.75 (d, 2H, J = 8.4Hz), 6.79 (t, 1H, J = 7.2 Hz), 6.98 (d, 2H, J = 8.8 Hz), 7.21-7.25 (m, 2H).

Compound 129



Compound 129 was prepared by General Method 9, by reduction of the nitro precursor which was made by general method General method 6.

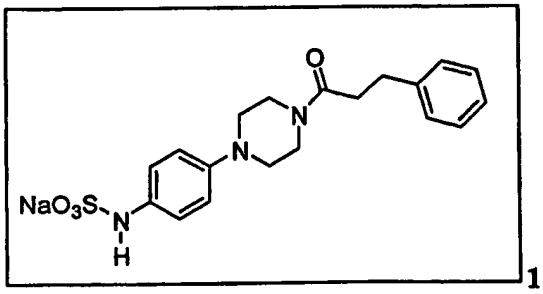
Data: HPLC: retention time 2.06 min. 97% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 3.56-3.58 (m, 4H), 3.71 (brs, 4H), 5.57 (s, 1H), 6.55 (d, 2H, J = 8.4 Hz), 6.63-6.65 (m, 1H), 7.03 (d, 1H, J = 3.6 Hz), 7.17 (d, 2H, 8.4 Hz), 7.85-7.86 (m, 1H).

Analytical Data for representative Sulfamic Acid Sodium Salts:

Compound 1: {4-[4(3-Phenyl-propionyl)-piperazin-1-yl]-phenyl}-sulfamic acid (sodium salt)

Compound 1 was prepared from compound 95 by General method B.

Data; HPLC: retention time 3.18 min; ^{1}H NMR (400 MHz, DMSO-d_6); 2.69 (t, 3H), 2.75 (m, 6H), 3.56 (m, 4H), 6.68 (d, 2H, J = 8.5), 6.92 (d, 2H, J = 8.56), 7.14 (m, 1H), 7.23 (m, 4H), 7.35 (s, 1H).

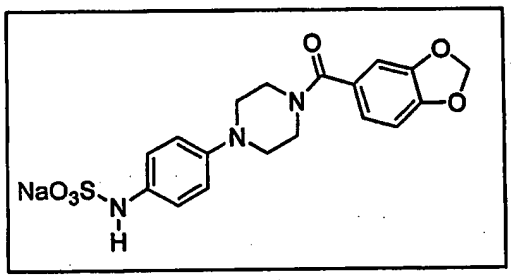


1

Compound 3: {4-[4-(Benzo[1,3]dioxole-5-carbonyl)-piperazin-1-yl]-phenyl}-sulfamic acid (sodium salt)

Compound 3 was prepared from compound 123 by General method B.

Data; HPLC: retention time 1.85 min; ^{1}H NMR (400 MHz, DMSO-d_6); 2.85 (br s, 4H), 3.50 (br s, 4H), 6.00 (s, 2H), , 6.75 (d, 2H, J = 8.5), 6.70-7.10 (m, 5H), 7.40 (s, 1H).

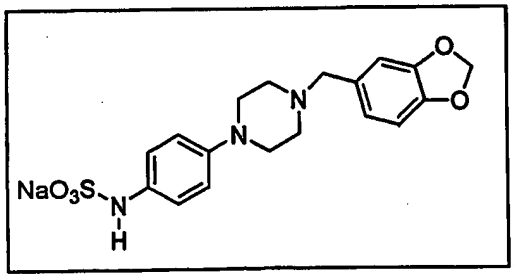


3

Compound 4: [4-(4-(Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Compound 3 was prepared by General method B, from compound 124.

Data; HPLC: retention time 2.02 min; ^{1}H NMR (400 MHz, DMSO-d_6); 2.42 (br s, 4H), 2.90 (br s, 4H), 3.37 (s, 2H), 5.95 (s, 2H), 6.62-6.95 (m, 7H), 7.26 (s, 1H).

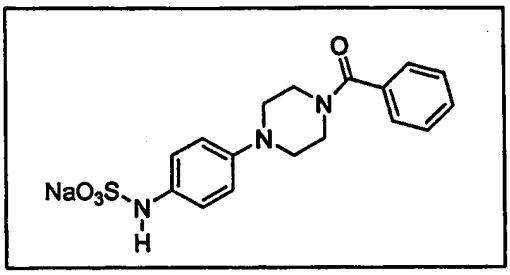


4

Compound 5: [4-(4-(Benzoyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Compound 5 was prepared by General method B, from compound 93.

Data; HPLC: retention time 2.59 min; ^{1}H NMR (400 MHz, DMSO-d_6); 2.95 (m, 4H), 3.42(m, 2H), 3.74 (m, 2H), 6.72 (d, 2H, J = 8.82), 6.93 (d, 2H, J = 8.82), 7.47-7.38 (m, 6H).

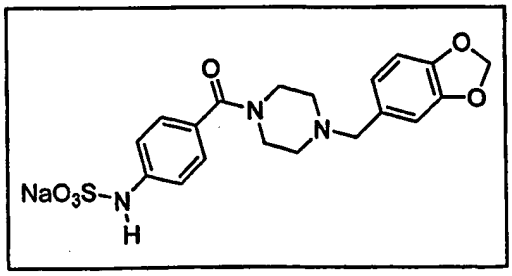


5

Compound 6: [4-(4-(Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-phenyl]-sulfamic acid (sodium salt)

Compound 6 was prepared from compound 125 using General method B.

Data; HPLC: retention time 1.79 min; ^{1}H NMR (400 MHz, DMSO-d_6); 2.36 (m, 4H), 3.45(s, 2H), 3.58(m, 2H), 5.96 (s, 2H), 6.73-6.82 (m, 3H), 6.95 (d, 2H), 7.18 (d, 2H), 8.23 (s, 1H).

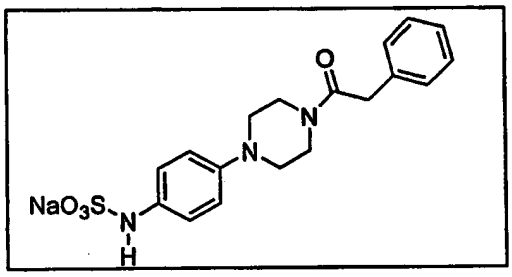


6

Compound 7: [4-(4-Phenylacetyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Compound 5 was prepared by General method B, from the aniline 94.

Data; HPLC: retention time 2.80 min; ^{1}H NMR (400 MHz, DMSO-d_6); 2.86 (m, 4H), 3.58(m, 4H), 3.78 (s, 2H), 6.62 (s, 2H), 6.93 (d, 2H), 7.32-6.95 (m, 5H), 7.39 (s, 1H).

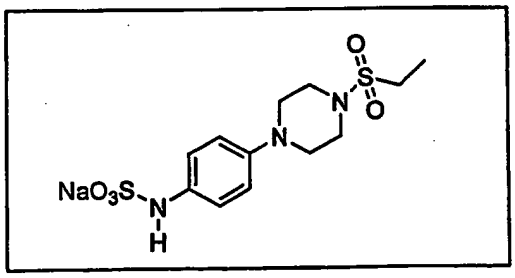


7

Compound 8: [4-(4-Ethanesulfonyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Compound 8 was prepared by General method B, from the aniline 126.

Data; HPLC: retention time 1.09 min; ^{1}H NMR (400 MHz, DMSO-d_6); 1.22 (t, 3H), 3.04(m, 4H), 3.19 (q, 2H), 3.34 (m, 4H), 6.78 (d, 2H), 6.95 (d, 2H), 7.40 (s, 1H).

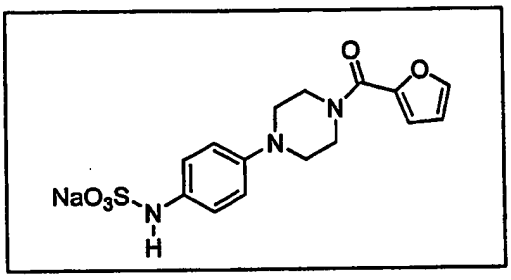


8

Compound 9: [4-(4-(Furan-2-carbonyl)-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Compound 9 was prepared by General method B, from the aniline 96.

Data; HPLC: retention time 1.21 min; ^{1}H NMR (400 MHz, DMSO-d_6); 2.95 (m, 4H), 3.75 (m, 4H), 6.59 (m, 1H), 6.72 (d, 2H), 6.88 (d, 2H), 6.95 (m, 1H), 7.36 (br s, 1H), 7.82 (s, 1H).

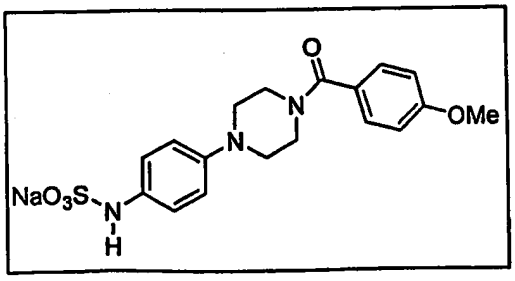


9

Compound 10: [4-(4-(4-Methoxy-benzoyl)-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Compound 10 was prepared using General method B from aniline 92.

Data; HPLC: retention time 1.96 min; ^{1}H NMR (400 MHz, DMSO-d_6); 2.85 (m, 4H), 3.58 (m, 4H), 3.78 (s, 3H), 6.72 (d, 2H), 6.98-6.91 (m, 4H), 7.35 (s, 1H), 7.36 (br s, 1H), 7.39 (d, 2H).

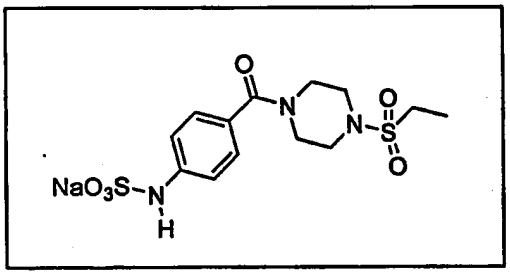


10

Compound 11: [4-(4-Ethanesulfonyl-piperazine-1-carbonyl)-phenyl]-sulfamic acid (sodium salt)

Compound 11 was prepared by General method B, from the aniline 127.

Data: HPLC: retention time 1.45 min; ^{1}H NMR (400 MHz, DMSO-d_6); 1.22 (t, 34H), 3.18 (q, 3H), 3.21 (m, 4H), 3.59 (m, 4H), 7.12 (d, 2H), 7.18 (d, 2H), 8.21 (s, 1H).

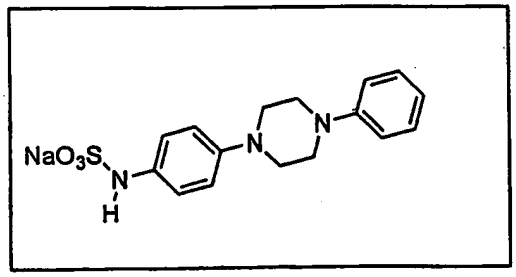


11

Compound 12: [4-(4-Phenyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Compound 12 was prepared by General method B, from the aniline 128. Compound 12 was prepared using General method B.

Data; HPLC: retention time 2.29 min; ^{1}H NMR (400 MHz, DMSO-d_6); 3.16 (m, 4H), 3.28 (m, 4H), 6.79-6.81 (m, 3H), 6.96-7.00 (m, 4H), 7.21-7.25 (m, 2H), 7.37 (s, 1H).

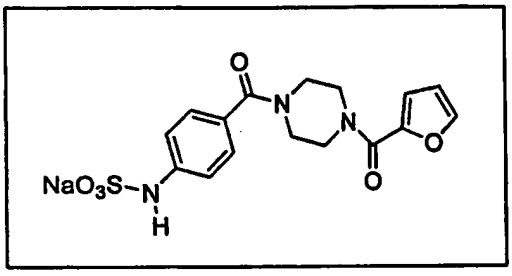


12

Compound 13: [4-(4-(Furan-2-carbonyl)-piperazine-1-carbonyl)-phenyl]-sulfamic acid (sodium salt)

Compound 13 was prepared by General method B, from the aniline 129.

Data; HPLC: retention time 1.75 min; ^{1}H NMR (400 MHz, DMSO-d_6); 3.54 (m, 4H), 3.67 (m, 4H), 6.60-6.59 (m, 1H), 6.96-7.00 (m, 4H), 7.02 (d, 2H), 7.18 (d, 2H), 7.81 (m, 1H), 8.26 (s, 1H).

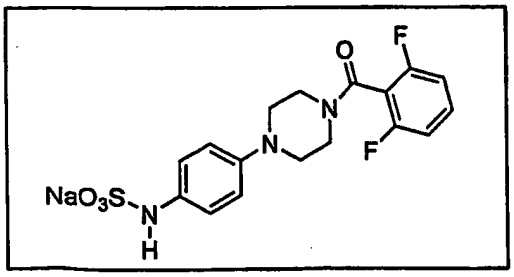


13

Compound 15: [4-(4-(2,6-Difluoro-benzoyl)-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Compound 15 was prepared by General method B, from the aniline 91.

Data; HPLC: retention time 1.84 min; ^{1}H NMR (400 MHz, DMSO-d_6); 2.98-2.82 (m, 2H), 3.18-3.15 (m, 4H), 3.82 (m, 2H), 6.78 (d, 2H), 7.18 (d, 2H), 7.21 (m, 2H), 7.56 (m, 1H), 7.96 (s, 1H).

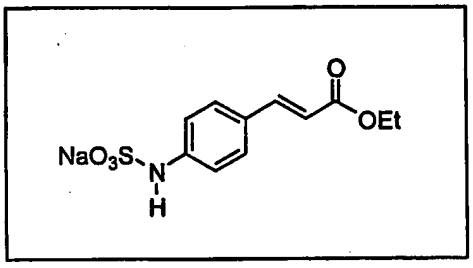


15

Compound 16: 3-(4-Sulfoamino-phenyl) acrylic acid ethyl ester (sodium salt)

Compound 16 was prepared using General method B from the corresponding commercial aniline.

Data; ^{1}H NMR (400 MHz, DMSO-d_6); 1.22 (t, 3H), 4.16 (q, 2H), 6.34 (d, 1H), 6.98 (d, 2H), 7.42 (d, 2H), 7.48 (d, 1H), 8.42 (1H).

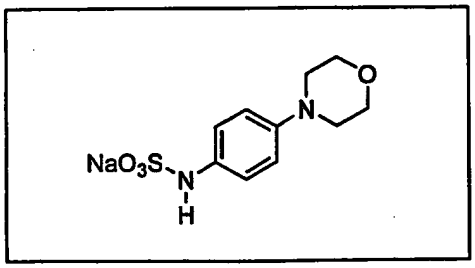


16

Compound 17: (4-Morpholin-4-yl-phenyl)-sulfamic acid (sodium salt)

Compound 17 was prepared using General method B from the corresponding commercial aniline.

Data; 1H NMR (400 MHz, DMSO-d_6); 2.91 (m, 4H), 3.72 (m, 2H), 6.72 (d, 2H), 6.98 (d, 2H), 7.39 (1H).

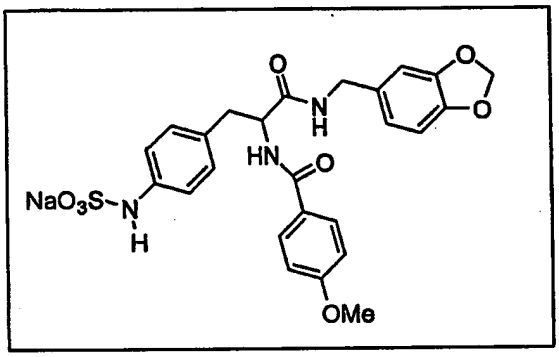


17

Compound 38: {4-[2-[(Benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-2-(4-methoxy-benzoylamino)-ethyl]-phenyl}-sulfamic acid (sodium salt)

Compound 38 was prepared using General method B.

Data; HPLC: retention time 3.22 min; ^{1}H NMR (400 MHz, DMSO-d_6); 2.96-2.82 (m, 2H), 3.80 (s, 3H), 4.2 (t, 2H, J = 4.0), 4.59-4.56 (m, 1H), 5.98 (s, 2H), 6.67 (d, 1H, J = 8.0), 6.92-6.82 (m, 4H), 7.02-6.96 (m, 4H), 7.66 (s, 1H), 7.80 (d, 2H, J = 8.4), 8.32 (d, 1H, J = 8.4), 8.48 (t, 1H, J = 5.6).

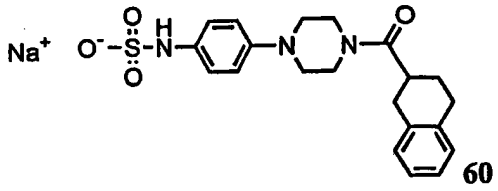


38

Compound 60: {4-[4-(1,2,3,4-Tetrahydro-naphthalene-2-carbonyl)-piperazin-1-yl]-phenyl}-sulfamic acid (sodium salt)

Compound 60 was prepared by General method B, from the aniline113.

Data: HPLC: retention time 2.94 min, 100% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 1.67 (m, 1H), 1.92 (m, 1H), 2.87 (m, 4H), 2.96 (m, 4H), 3.06 (m, 1H), 6.76 (d, 2H, J=8.8), 6.96 (d, 2H, J=8.8), 7.08 (s, 4H), 7.39 (s, 1H).

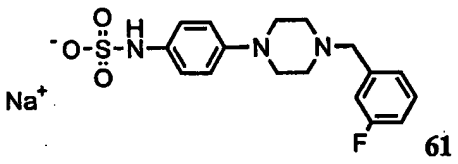


60

Compound 61: {4-[4-(3-Flouro-benzyl)-piperazin-1-yl]-phenyl}-sulfamic acid (sodium salt)

Compound 61 was prepared by General method B, from the aniline 114.

Data: HPLC: retention time 2.00 min, 98% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.97 (m, 4H), 3.53 (s, 2H), 6.71 (d, 2H, J=8.4), 6.94 (d, 2H, J=8.8), 7.08 (m, 1H), 7.16 (m, 2H), 7.29 (s, 1H), 7.37 (m, 1H).

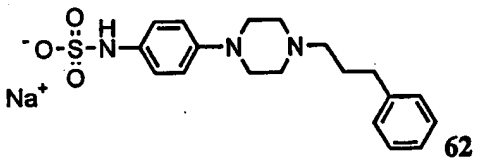


61

Compound 62: {4-[4-(3-Phenyl-propyl)-piperazin-1-yl]-phenyl}-sulfamic acid (sodium salt)

Compound 62 was prepared by General method B, from the aniline 115.

Data: HPLC: retention time 2.62 min, 94% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 1.74 (m, 3H), 2.31 (m, 4H), 2.60 (m, 3H), 2.95 (m, 4H), 6.70 (d, 2H, J=8.8), 6.94 (d, 2H, J=9.2), 7.21 (m, 6H).

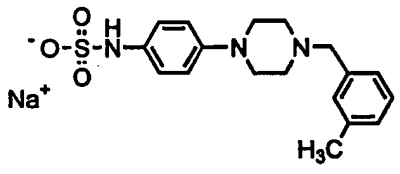


62

Compound 63: {4-[4-(3-Methyl-benzyl)-piperazin-1-yl]-phenyl}-sulfamic acid (sodium salt)

Compound 63 was prepared by General method B, from the aniline 116.

Data: HPLC: retention time 2.29 min, 97% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.23 (s, 3H), 2.50 (s, br, 4H), 2.96 (s, br, 4H), 3.46 (s, 2H), 6.70 (d, 2H, J=8.8), 6.94 (d, 2H, J=8.8), 7.09 (m, 3H), 7.21 (m, 1H), 7.28 (s, 1H).

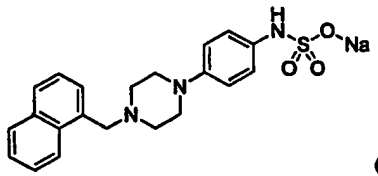


63

Compound 64: [4-(4-Naphthalen-1-ylmethyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Compound 64 was prepared using General method B from aniline 109.

Data; ^{1}H NMR (400 MHz, DMSO-d_6); 2.54 (m, 4H), 2.91 (m, 4H), 3.89 (s, 2H), 6.67 (d, 2H, J = 8.8), 6.91 (d, 2H, J = 8.8), 7.28 (s, 1H), 7.41-7.52 (4H), 7.82 (m, 2H), 7.89 (d, 1H, J = 7.6), 8.27 (d, 1H, J = 8.0)

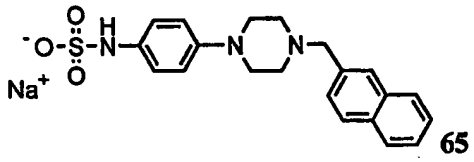


64

Compound 65: [4-(4-Naphthalen-1-ylmethyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Compound 65 was prepared by General method B, from the aniline 121.

Data: HPLC: retention time 1.98 min, 92% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.56 (m, 4H), 2.89 (m, 4H), 3.61 (s, 2H), 6.62 (d, 2H, J = 8.2 Hz), 6.91 (d, 2H, J = 8.2Hz), 7.32 (s, 1H), 7.54-7.39 (m, 3H), 7.79 (s,1H), 7.84 (brs, 3H).

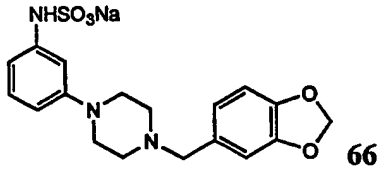


65

Compound 66: [3-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Compound 66 was prepared using General method B, from aniline 101.

Data: HPLC: retention time 1.74 min, 94% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.42 (m, 4H), 2.98 (m, 4H), 3.42 (s, 2H), 5.98(s, 2H), 6.23 (d, 1H), 6.45 (d, 1H), 6.62-6.98 (m, 4H), 7.58 (s,1H).

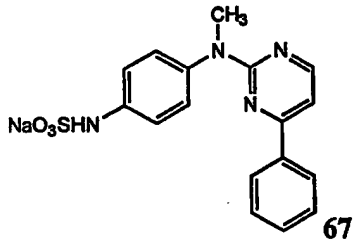


66

Compound 67: {4-[Methyl-(4-phenyl-pyrimidin-2-yl)-amino]-phenyl}-sulfamic acid (sodium salt)

Compound 67 was synthesized from aniline 108 using General method B.

Data for 67; HPLC: retention time 2.99 min, 96% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 3.44 (2 pair of singlets, 3H), 7.4 (m, 3H), 7.25 (m, 2H), 7.47 (m, 3H), 8.04 (m, 2H), 8.36 (2 pair of doublets, J = 5.2 Hz, 1H).

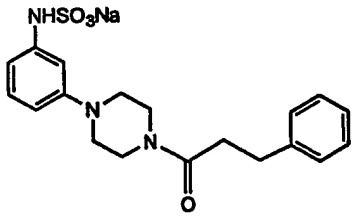


67

Compound 68: [3-(4-(3-Phenyl-propionyl)-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Compound 68 was prepared using General method B from aniline 104.

Data: ^{1}H NMR (400 MHz, DMSO-d_6); 2.61 (t, J = 8 Hz, 2H), 2.92 (t, J = 8 Hz, 2H), 2.94 (m, 4H), 3.55 (m, 4H), 6.25 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 8 Hz, 1H), 6.68 (m, 1H), 6.89 (t, J = 8 Hz, 1H), 7.21 (m, 5H), 7.60 (s, 1H).

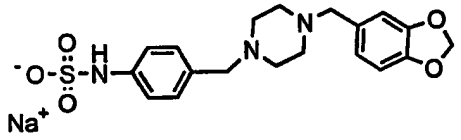


68

Compound 69: [4-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-phenyl]-sulfamic acid (sodium salt)

Compound 69 was made by General method B, from aniline 120.

Data: HPLC: retention time 1.44 min, 95% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.36 (brs, 6H), 2.98 (m, 4H), 3.22 (s, 2H), 3.38(brs, 4H), 5.96 (s, 2H), 6.71 (dd, 1H), 6.82 (m, 2H), 6.98-6.95(brs, 4H), 7.74 (s, 1H).

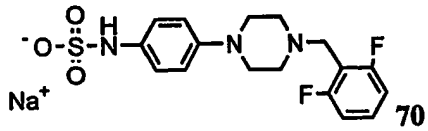


69

Compound 70: {4-[4-(2,6-Diflouro-benzyl)-piperazin-1-yl]-phenyl}-sulfamic acid (sodium salt)

Compound 70 was prepared by General method B, from the aniline 117.

Data: HPLC: retention time 1.79 min, 85% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 2.82 (s, br, 4H), 3.14 (s, br, 4H), 3.92 (s, br, 2H), 6.88 (m, 3H), 7.18 (m, 2H), 7.51 (m, 1H).

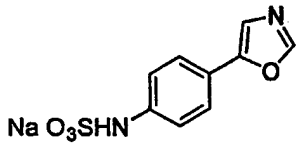


70

Compound 71: (4-Oxazol-5-yl-phenyl)-sulfamic acid (sodium salt)

Compound 71 was prepared using General method B from aniline 118.

Data: HPLC: retention time 1.54 min, 94% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 7.09 (d, 2H, J=8.4), 7.38 (s, 1H), 7.44 (d, 2H, J=8.4), 8.20 (s, 1H), 8.29 (s, 1H).

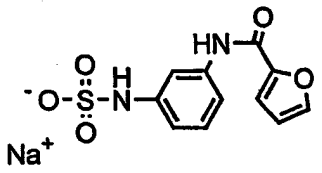


71

Compound 72: {3-[(Furan-2-carbonyl)amino]-phenyl}-sulfamic acid (sodium salt)

Compound 72 was prepared using General method B from aniline 122.

Data: HPLC: retention time 1.50 min, 100% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 6.67 (dddd,1H), 6.79-6.81(m, 1H), 7.01 (t, 1H, *J*= 8.0 Hz), 7.13-7.15 (m, 1H), 7.26 (t, 1H, J = 2.0 Hz), 7.36 (d, 1H, J = 3.2 Hz), 7.86 (s, 1H), 7.89 (m, 1H), 9.98 (s, 1H).

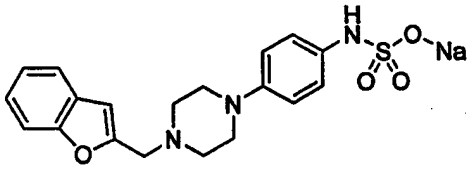


72

Compound 73: [4-(4-Benzofuran-2-ylmethyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Compound 73 was prepared using General method B from aniline 110.

Data: ^{1}H NMR (400 MHz, DMSO-d_6); 2.57 (m, 4H), 2.94 (m, 4H), 3.69 (s, 2H), 6.67 (d, 2H, J = 8.8), 6.77 (s, 1H), 6.90 (d, 2H, J = 8.8), 7.16-7.26 (2H), 7.28 (s, 1H), 7.52 (d, 1H, J = 8.0), 7.56 (dd, 1H, J = 7.6 and 0.8)

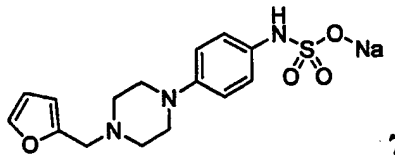


73

Compound 74: [4-(4-Furan-2-ylmethyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Compound 74 was prepared using General method B from aniline 111.

Data: ^{1}H NMR (300 MHz, DMSO-d_6); 2.42 (m, 4H), 2.87 (m, 4H), 3.45 (s, 2H), 6.22 (m, 1H), 6.32 (m, 1H), 6.62 (d, 2H, J = 9.0), 6.86 (d, 2H, J = 9.0), 7.27 (s, 1H), 7.51 (m, 1H).

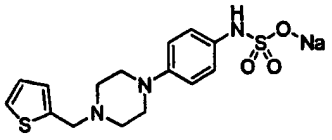


74

Compound 75: [4-(4-Thiophen-2-ylmethyl-piperazin-1-yl)-phenyl]-sulfamic acid (sodium salt)

Compound 75 was prepared using General method B from aniline 112.

Data; ^{1}H NMR (300 MHz, DMSO-d_6); 2.44 (m, 4H), 2.88 (m, 4H), 3.64 (s, 2H), 6.62 (d, 2H, J = 9.3), 6.85 (d, 2H, J = 9.3), 6.89-6.90 (2H), 7.23 (s, 1H), 7.36 (dd, 1H, J = 4.8 and 1.8).

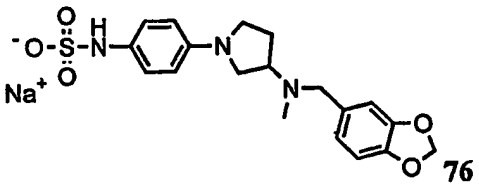


75

Compound 76: {4-[3-(Benzo[1,3]dioxol-5-ylmethyl-methyl-amino)-pyrrolidin-1-yl]-phenyl}-sulfamic acid
(sodium salt)

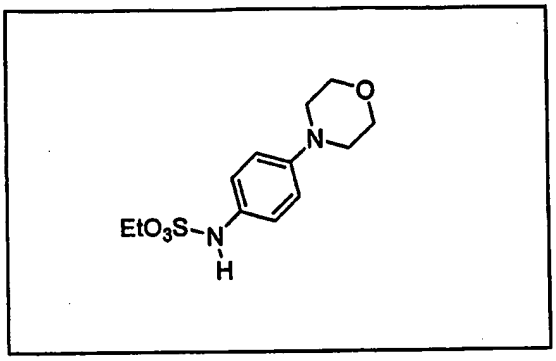
Compound 76 was prepared by General method B, from the aniline 119.

Data: HPLC: retention time 1.98 min, 92% at 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6); 1.89 (m, 1H), 2.07 (s, 3H), 2.13 (m, 1H), 3.10 (m, 4H), 3.43 (s, 3H), 5.99 (m, 2H), 6.38 (d, 2H, J=8.8), 6.87 (m, 6H).



76

Compound 57: (4-Morpholin-4-yl-phenyl)-sulfamic acid ethyl ester



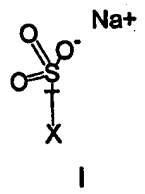
57

To a solution of 4-morpholinoaniline (1 equiv.) in CH_2Cl_2(~0.1mmol) cooled to 0°C was added *p*-nitrophenylsulfonyl chloride (1.5 equiv.) in a minimum of CH_2Cl_2 and Et_3N (1.5 equiv.). The reactions stirred at room temperature for 2-5 hrs., then EtOH (5 equiv.) and Et_3N (5 equiv.) was added and the mixture was stirred for 12-24 hrs. The reaction mixture was checked by TLC using 2:1 EtOAc/Hex. Reaction mixture was washed with water and brine, concentrated and purified using prep. TLC (2X) using 2:1 EtOAc/Hex and then 2:1 Hex/EtOAc.

1H NMR : 1.35 (t, 3H), 3.1 (dd, 4H), 3.82 (dd, 4H), 4.21 (q, 2H), 6.85 (d, 2H), 7.15 (d, 2H).

What is claimed is:

1. A compound of the structural formula (I)



I

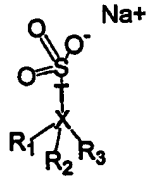
or a pharmaceutically acceptable salt, ester, solvate or prodrug thereof

wherein
T is NH or NHNH,
and X is defined as described in A, B, and C below:

A. when X is aryl as in formula II, aryl is selected from the group consisting of unsubstituted and mono-, di-, and tri-substituted phenyl, pyridyl, pyrimidyl, indanyl, indolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, or 9*H*-carbazole,

R_1, R_2 and R_3 are attached directly to the aryl group or attached via a linking moiety selected from the group consisting of amido (-CONH-R_4 or –NHCO-R_4), thioamido (-CSNH-R_4 or –NHCS-R_4), carboxyl (-CO_2-R_4), carbonyl (-CO-R_4), urea (-NHCONH-R_4), thiourea (-NHCSNH-R_4), sulfonamido, (-$NHSO_2$-R_4 or -SO_2NH-R_4), ether (-O-R_4), amino (-N(R_4)R_4'), sulfonyl (-SO_2-R_4), and sulfoxyl (-SO-R_4),

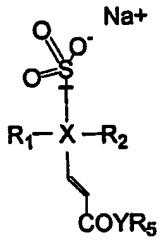
wherein R_1, R_2 and R_3 are independently selected from the group consisting of :



II

(i) hydrogen, carbonyl, halo, hydroxy, nitro, trihalomethyl, cyano, branched and unbranched C_{1-8} alkyl, C_{1-8} alkylaryl, C_{3-8} cycloalkyl, fused C_{3-8} cycloalkyl, C_{0-8}alkyloxyC_{1-6}alkyl, C_{0-8}alkylcarboxyC_{1-6}alkyl, C_{0-6} alkyloxyC_{0-3} alkylaryl, methylenedioxy, and R_4, wherein R_4 and R4' are selected from the group consisting of

(a) Hydrogen, substituted or unsubstituted C_{1-8} alkyl, C_{0-6} alkylaryl, C_{1-6} alkyloxyC_{1-3} alkyl, C_{0-6} alkylcarboxyC_{1-6} alkyl, C_{0-6} alkyloxyC_{0-3} alkylaryl, C_{0-3}alkylarylaryl in which said aryl is selected from the group consisting of phenyl, isoxazolyl, pyrazolyl, imidazolyl, thiazolyl, pyridyl, pyrimidyl or benzthiazolyl, and in which the substituents are selected from the group consisting of (a), C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-3} alkyl, halo, hydroxy, nitro, trihalomethyl, and cyano;



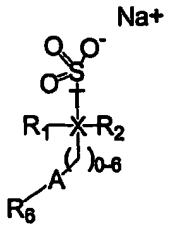
III

B. when X is aryl as formula III, Y is N or O, and aryl is selected from the group consisting of unsubstituted or mono-, di- and tri-substitute phenyl, pyridyl, pyrimidyl, indanyl, indolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, or 9*H*-carbazole

where the substituents, R_1, R_2, are attached directly to the aryl group or attached by a linking moiety selected from the group consisting of amido (-CONH-R_{1or2} or –NHCO-R_{1or2}), thioamido (-CSNH- R_{1or2} or –NHCS- R_{1or2}), carboxyl (-CO_2-R_{1or2}), carbonyl (-CO-R_{1or2}), urea (-NHCONH-R_{1or2}), thiourea (-NHCSNH-R_{1or2}), sulfonamido, (-$NHSO_2$-R_{1or2} or -SO_2NH- R_{1or2}), ether (-O-R_{1or2}), sulfonyl (-SO_2-R_{1or2}), and sulfoxyl (-SO-R_{1or2}),

where R_1, R_2 are independently selected from A(i) above and R_5 is selected from

(i) substituted and unsubstituted C_{1-6} alkyl, and C_{0-6} alkylaryl, where aryl is selected from the group consisting of unsubsituted and mono, di and tri- substituted biphenyl, phenyl, indolyl, pyridyl, pyrimidyl, indanyl, indolyl, benzthiazole, thiazolyl, imidazolyl, oxazolyl, and isoxazolyl, wherein the substituents are selected from A(i) above;



IV

C. when X is aryl as in formula IV, T is NH or NHNH, aryl is selected from meta and/or para, mono, di and tri, substituted or unsubstituted phenyl, pyridyl, pyrimidyl, or mono, di or tri-substituted or unsubstituted indanyl, indolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, or 9*H*-carbazole

wherein one or both of substituents, R_1 , R_2, are attached directly to the aryl group or attached by a linking moiety selected from the group consisting of amido (-CONH-R_{1or2} or –NHCO- R_{1or2}), thioamido (-CSNH- R_{1or2} or –NHCS- R_{1or2}), carboxyl (-CO_2- R_{1or2}), carbonyl (-CO- R_{1or2}), urea (-NHCONH- R_{1or2}), thiourea (-NHCSNH- R_{1or2}), sulfonamido, (-$NHSO_2$- R_{1or2} or -SO_2NH- R_{1or2}), ether (-O- R_{1or2}), sulfonyl (-SO_2- R_{1or2}), or sulfoxyl (-SO- R_{1or2}), and wherein R_1 and R_2 are independently selected from A(i) above;

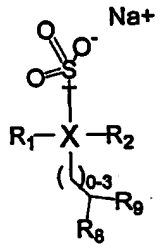
wherein A is selected from unsubstituted or substituted morpholino, piperidino, piperazino, pyrrolidino, prolyl, pyrrolidinonyl, hydantoinyl, and diketopiperazinyl;

wherein R_6 is selected from the group consisting of:

(i) hydroxy, carbonyl, branched and unbranched C_{1-8} alkyl, C_{3-8} cycloalkyl, fused C_{3-8} cycloalkyl, C_{0-8}alkyloxyC_{1-6}alkyl, C_{0-8}alkylcarboxyC_{1-6}alkyl, C_{0-6} alkyloxyC_{0-3} alkylaryl, and R_7, where R_7 is attached directly or attached via a linking moiety selected from the group consisting of amido (-CONH-R_7 or –NHCO-R_7, or NCO-R_7 if bound via a

ring nitrogen of A, e.g. in piperazine), thioamido (-CSNH-R_7 or –NHCS-R_7), carboxyl (-CO_2-R_7), carbonyl (-CO-R_7), urea (-NHCONH-R_7), thiourea (-NHCSNH-R_7), sulfonamido, (-$NHSO_2$-R_7 or -SO_2NH-R_7), ether (-O-R_7), amino (N(R_7)$R_{7'}$), sulfonyl (-SO_2-R_7), and sulfoxyl (-SO-R_7) where R_7 is selected from the group consisting of:

(a) substituted or unsubstituted C_{1-8} alkyl, C_{0-6} alkylaryl, C_{0-6} alkyloxyC_{1-3} alkyl, C_{0-6} alkylcarboxyC_{1-6} alkyl, C_{0-6} alkyloxyC_{0-3} and alkylaryl where aryl is selected from the group consisting of phenyl, isoxazolyl, pyrazolyl, imidazolyl, thiazolyl, furyl, thienyl, pyridyl, naphthyl, tetrahydronaphthyl, benzfuryl and benzthiazolyl, wherein the substituents are selected from the group consisting of C_{1-6} alkyl, C_{0-3} alkyloxy C_{1-6} alkyl, halo, hydroxy, nitro, trihalomethyl, cyano, carboxyl, carboxylC_{1-4}alkylester, methylenedioxy (e.g. a benzo[1,3]dioxole moiety), branched and unbranched C_{1-8} alkyl, C_{3-8} cycloalkyl, and fused C_{3-8} cycloalkyl;



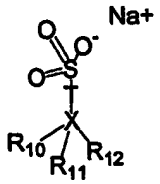
V

D. when X is aryl as in formula V, T is NH or NHNH, aryl is selected from the group consisting of unsubstituted or mono-, di- and tri- substituted phenyl, pyridyl, pyrimidyl, or mono, di or tri-substituted or unsubstituted indanyl, indolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, and 9*H*-carbazole,

where one or both substituents R_1 and R_2 are attached directly to the aryl group or attached via a linking moiety selected from the group consisting of amido (-CONH-R_{1or2} or –NHCO- R_{1or2}), thioamido (-CSNH- R_{1or2} or –NHCS- R_{1or2}), carboxyl (-CO_2- R_{1or2}), carbonyl (-CO- R_{1or2}), urea (-NHCONH- R_{1or2}), thiourea (-NHCSNH- R_{1or2}), sulfonamido, (-$NHSO_2$- R_{1or2} or -SO_2NH- R_{1or2}), ether (-O- R_{1or2}), sulfonyl (-SO_2- R_{1or2}), and sulfoxyl (-SO- R_{1or2}),

wherein R_1 and R_2 are independently selected from A(i) above,

wherein R_8 and R_9 are independently selected A(i) above, and wherein R_8 and R_9 are independently attached directly or attached via a linking moiety selected from the group consisting of amido (-CONH-R_{8or9} or –NHCO- R_{8or9}), thioamido (-CSNH-R_{8or9} or –NHCS- R_{8or9}), carboxyl (-CO_2- R_{8or9}), carbonyl (-CO- R_{8or9}), urea (-NHCONH- R_{8or9}), thiourea (-NHCSNH- R_{8or9}), sulfonamido, (-$NHSO_2$- R_{8or9} or -SO_2NH- R_{8or9}), ether (-O- R_{8or9}), sulfonyl (-SO_2- R_{8or9}), and sulfoxyl (-SO- R_{8or9});



VI

E. when X is alkyl as in formula VI, and T is NH or NHNH, alkyl is selected from substituted or unsubstituted C_{1-6} alkyl, C_{1-6} alkyloxyC_{1-3} alkyl, C_{1-6} alkylaryl, C_{1-6} alkyloxyC_{0-3} alkylaryl, C_{3-8} cycloalkyl, piperidino, fused piperidino, C_{0-6} alkylC_{3-8}cycloalkyl, C_{0-6} alkyl morpholino, C_{0-6} alkyl piperidino, C_{0-6} alkyl piperizino, C_{0-6} alkyl pyrrolidino, wherein aryl is selected from the group consisting of unsubstituted and mono-di-, and tri- substituted phenyl, pyridyl, pyrimidyl, indanyl, thienyl, furyl, indolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl,

wherein the substituents R_{10}, R_{11} and R_{12} are independently selected from the group consisting (i), (ii) and (iii) below:

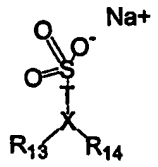
(i) hydrogen, halo, hydroxy, nitro, trihalomethyl, cyano, C_{0-6} alkyl carboxyC_{1-4} alkyl, C_{1-8} alkyl;

(ii) substituted or unsubstituted C_{1-8} alkyl, C_{0-6} alkylaryl, C_{0-6} alkyloxyC_{1-3} alkyl, methylenedioxy (e.g. a benzo[1,3]dioxole moiety), C_{0-6} alkylcarboxyC_{1-6} alkyl, C_{0-6} alkyloxyC_{0-3} alkylaryl where aryl is selected from phenyl, isoxazolyl, pyrazolyl,

imidazolyl, thiazolyl, pyridyl or benzthiazolyl, where the substituents are selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-3} alkyl, halo, hydroxy, nitro, trihalomethyl, and cyano, and attached directly to the aryl group or are attached via a linking moiety selected from the group consisting of amido, carboxyl, urea, and sulfonamido;

(iii) the compounds of A(i) above, said compounds attached directly to the aryl ring, or *via* a, linking moiety selected from the group consisting of amido, carboxy, urea, and sulfonamido.

2. A compound according to claim 1 having structural formula VII;



VII

or a pharmaceutically acceptable salt, ester, solvate, or prodrug thereof,

wherein X is defined as in A , B, and C below:

A. when T is NH, X is selected from the group consisting of unsubstituted or R_{13}-substituted phenyl, oxazolyl, isoxazolyl, piperidinyl, piperazinyl, substituted benzthienyl, indanyl, pyridyl, cyclohexyl, 9*H*-carbazole and benzo[1,3]dioxole,

wherein R_{13} is selected from the group consisting of substituted piperazino, pyrrolidino, halo, hydrogen, phenyl, branched or unbranched C_{1-6} alkyl, C_{1-3} alkyl phenyl, C_{0-2} alkyl carboxyC_{1-3} alkyl ester, oxyC_{1-6}alkyl, morpholino, oxyphenyl, C_{2-6} alkenylamidoR_{15}, C_{2-6} alkenylcarboxyR_{15}, or dimethylpyrimidine, said R_{13} attached directly to X or attached to X via a linking moiety selected from the group consisting of amide, sulfonamide, amino, ether or C_{1-3} alkyl,

wherein a substituent of R_{13} is R_{16}, wherein R_{16} is attached directly to R_{13} or attached to R_{13} via an amido (-CONH- R_{16} or –NHCO- R_{16}, or NCO- R_{16} if bound via a ring nitrogen of 'A" e.g. in piperazine), sulfonamido, (-$NHSO_2$- R_{16} or -SO_2NH- R_{16}), or amino ($N(C_{16})C_{16'}$) wherein R_{16} or $R_{16'}$ is selected from the group consisting of:

(i) hydrogen, substituted or unsubstituted C_{1-8} alkyl, C_{0-6} alkylaryl, C_{0-6} alkyloxyC_{1-3} alkyl, C_{0-6} alkylcarboxyC_{1-6} alkyl, and C_{0-6} alkyloxyC_{0-3} alkylaryl wherein aryl is selected from the group consisting of phenyl, furyl, tetrahydronaphthyl, naphthyl, thienyl, wherein the substituents are selected from the group consisting of C_{1-6} alkyl, C_{0-3} alkyloxy C_{1-6} alkyl, halo, methylenedioxy (e.g. a benzo[1,3]dioxole moiety), carboxy, carboxyalkylester, branched and unbranched C_{1-8} alkyl, C_{3-8} cycloalkyl, and fused C_{3-8} cycloalkyl;

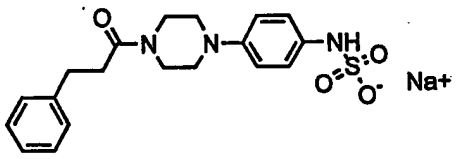
wherein R_{14} is attached directly to X or via a linking moiety selected from the group consisting of amide, sulfonamide and C_{1-3} alky on the meta-position of X, R_{14} selected from the group consisting of methoxy, bis-*meta*-methoxy, hydrogen, oxyphenyl, C_{1-3} alkyl, and oxybenzyl;

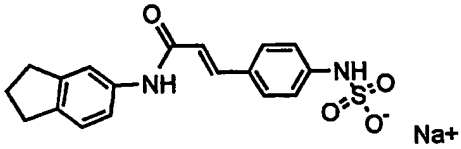
wherein R_{15} is selected from the group consisting of biphenyl, methyl, ethyl, benzyl, indanyl and p-methoxybenzyl;

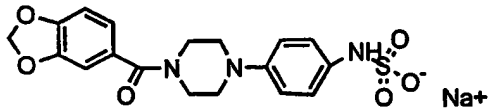
B. when T is NH, X is unsubstituted or substituted C_{1-6} alkyl, said substituent selected from the group consisting of phenyl, methoxy, morpholino, pyridyl, diphenyl, pyrrolidino, or thienyl;

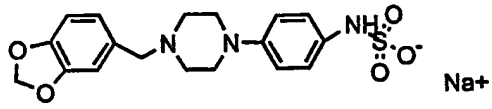
C. when T= NHNH, X is methylpiperazine, or p-methoxyphenyl.

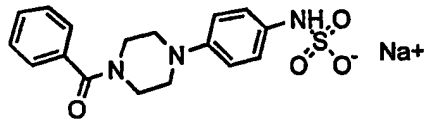
3. A compound according to claim 1, said compound selected from the group consisting of

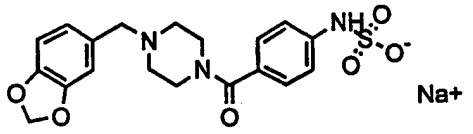


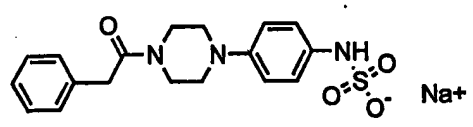


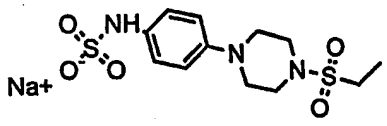


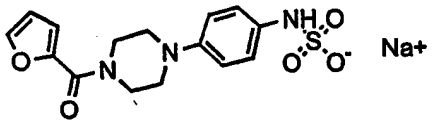


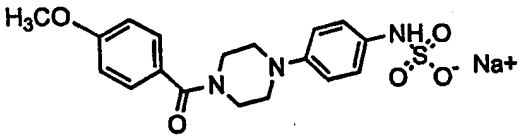


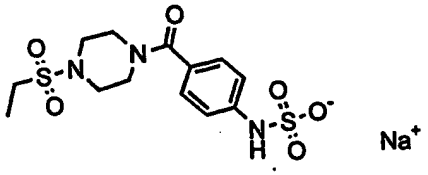


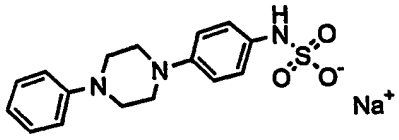


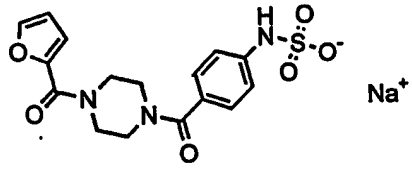


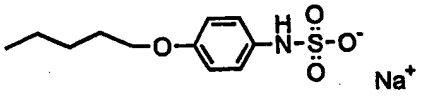


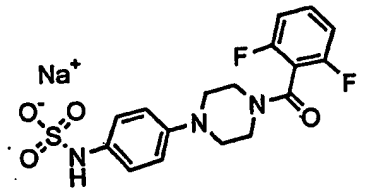


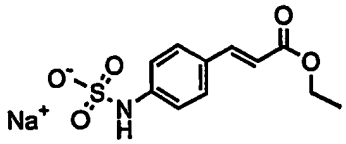


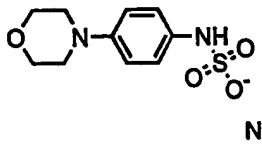


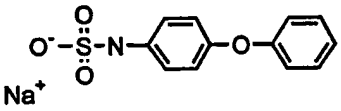


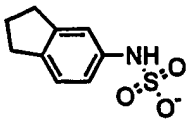


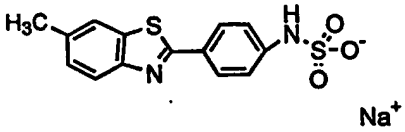


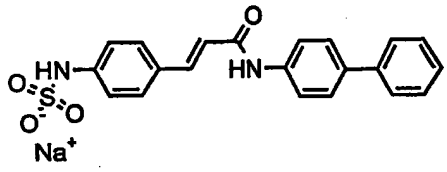


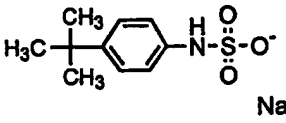


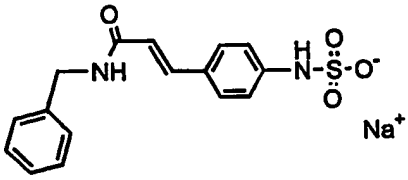


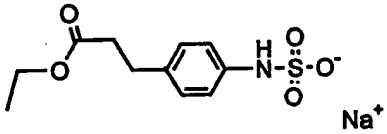


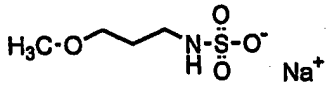


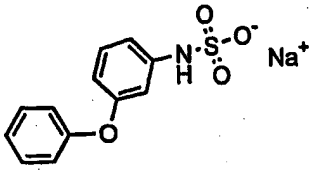


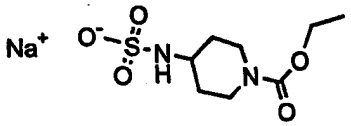


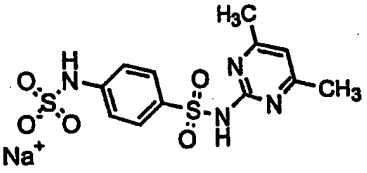


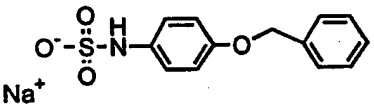


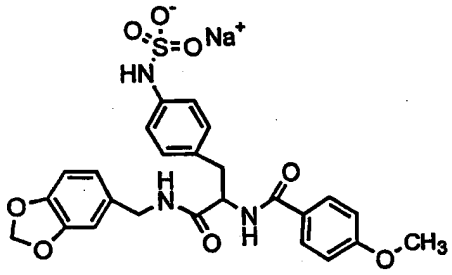


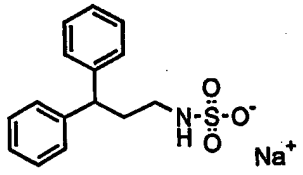


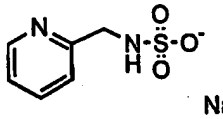


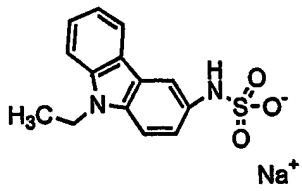


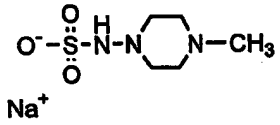


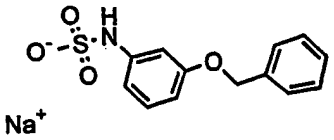


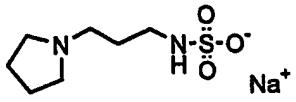


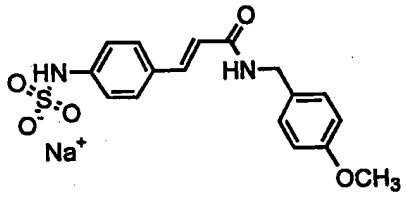


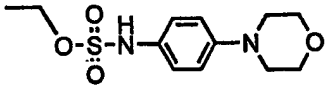


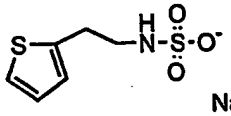


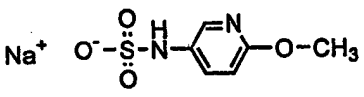


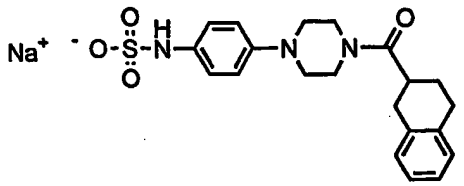


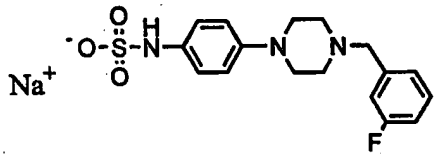


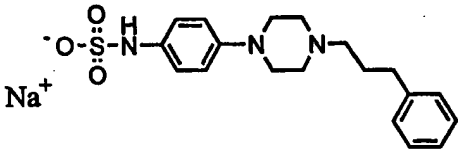


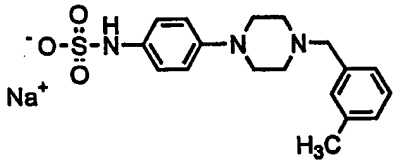


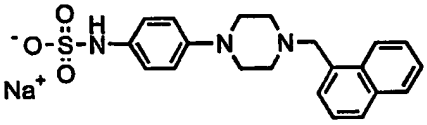


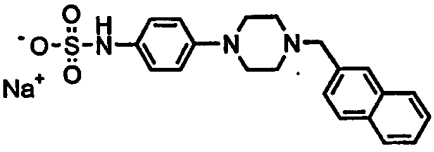


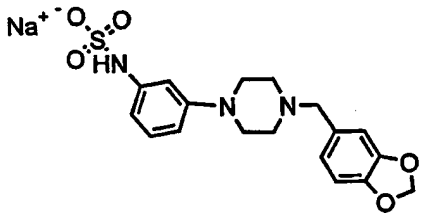


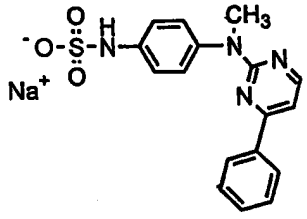


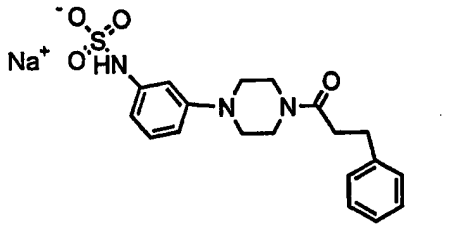


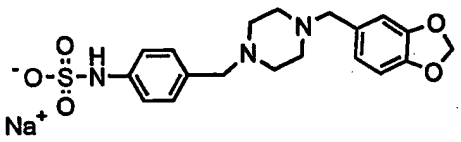


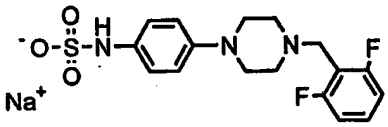


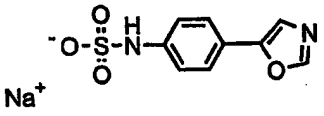


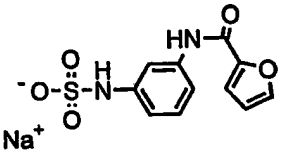


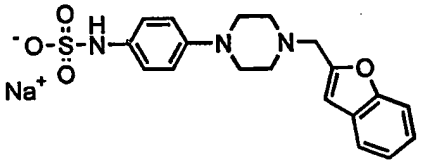


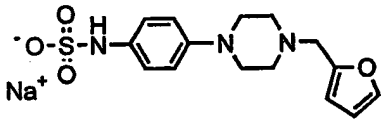


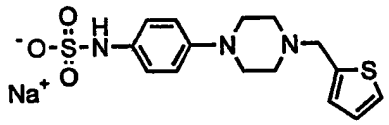


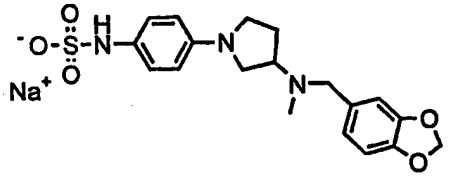




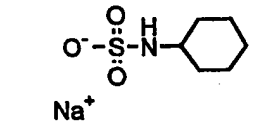


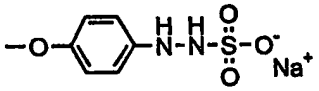


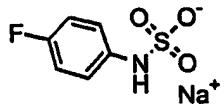


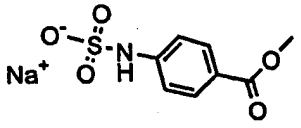


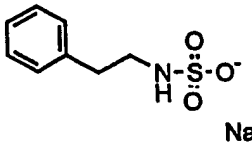
4. A compound according to claim 1 which is:

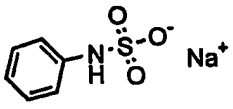


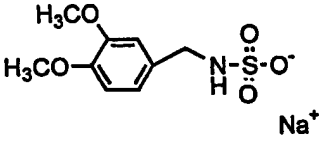


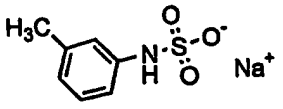


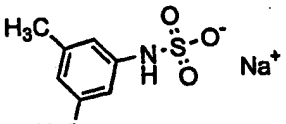


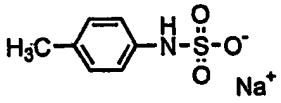


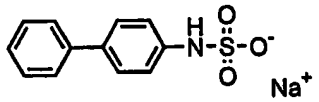


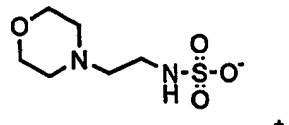


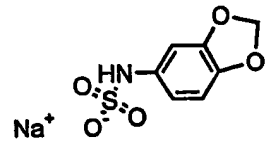


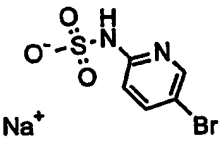


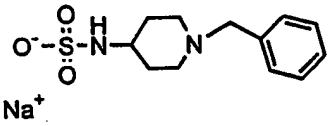


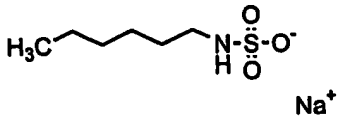


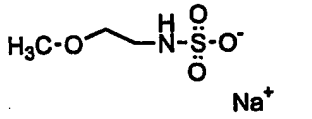




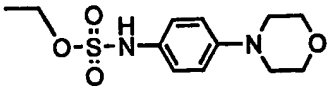




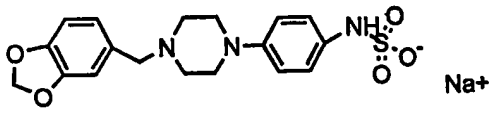




5. A compound according to claim 1, of the following structural formula:



6. A compound according to claim 1, of the following structural formula:



7. A pharmaceutical composition comprising one or more compounds according to claim 1, 2, 3, 5 or 6.

8. A method for treating wounds or tissue damage to accelerate healing in a subject, in a mammalian patient in need of such treatment comprising administering to said patient an effective amount of a compound of claim 1.

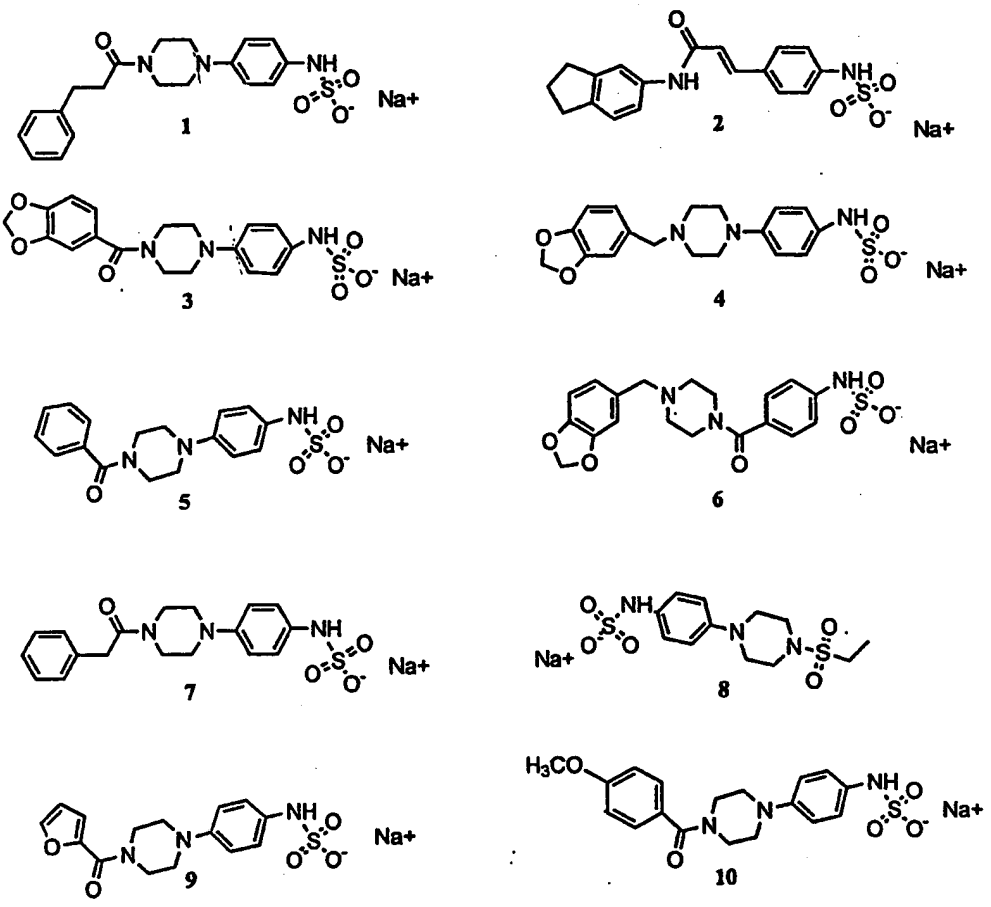


Figure 1

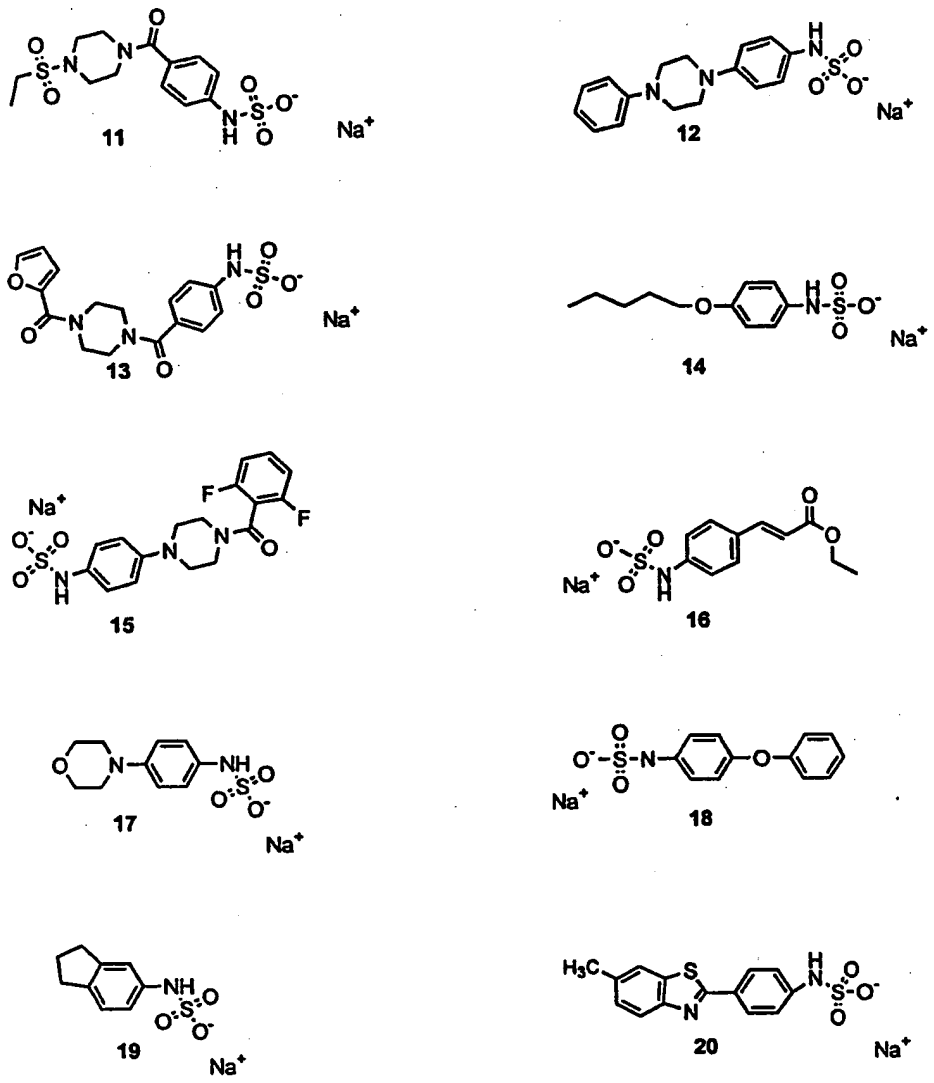


Figure 2

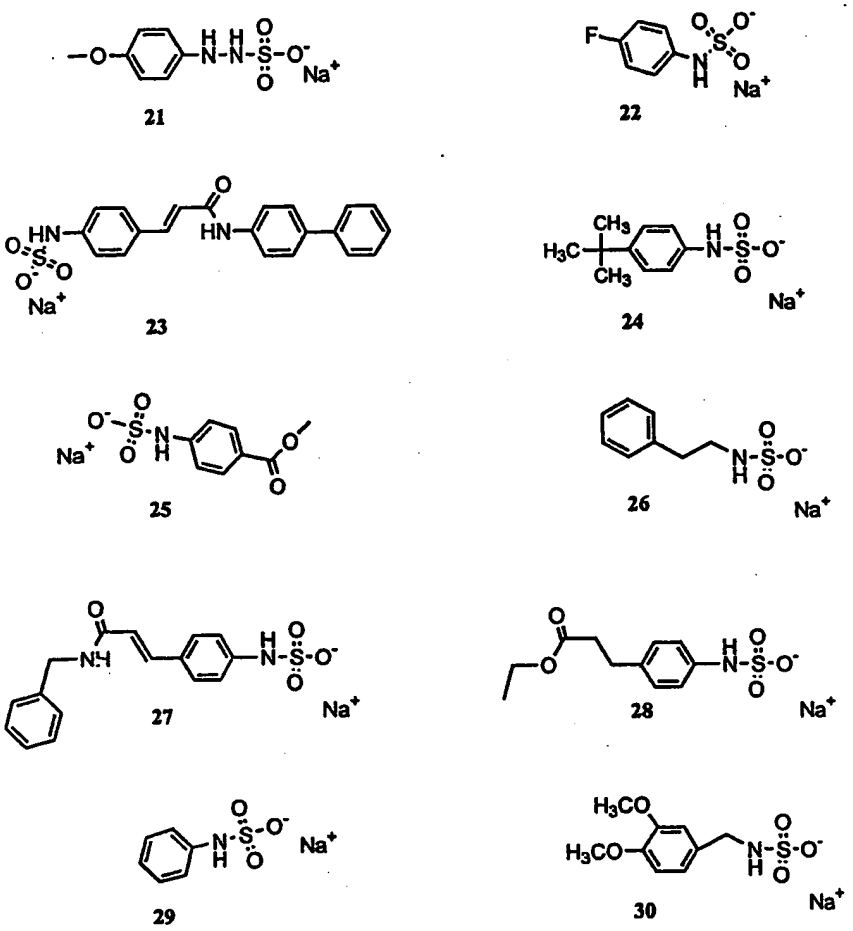


Figure 3

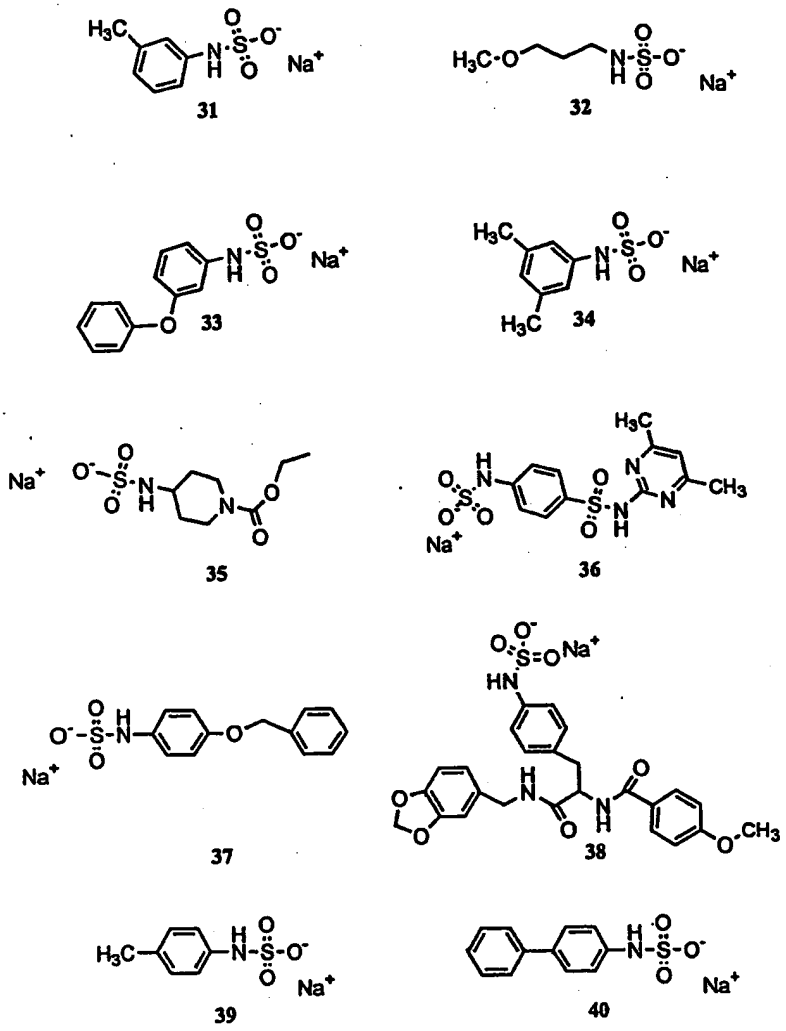


Figure 4

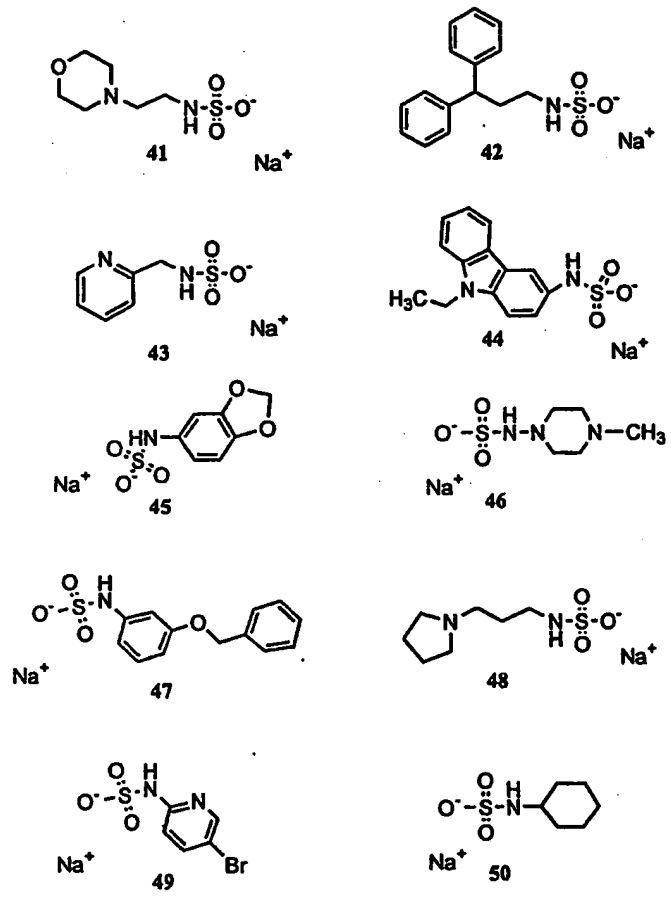


Figure 5

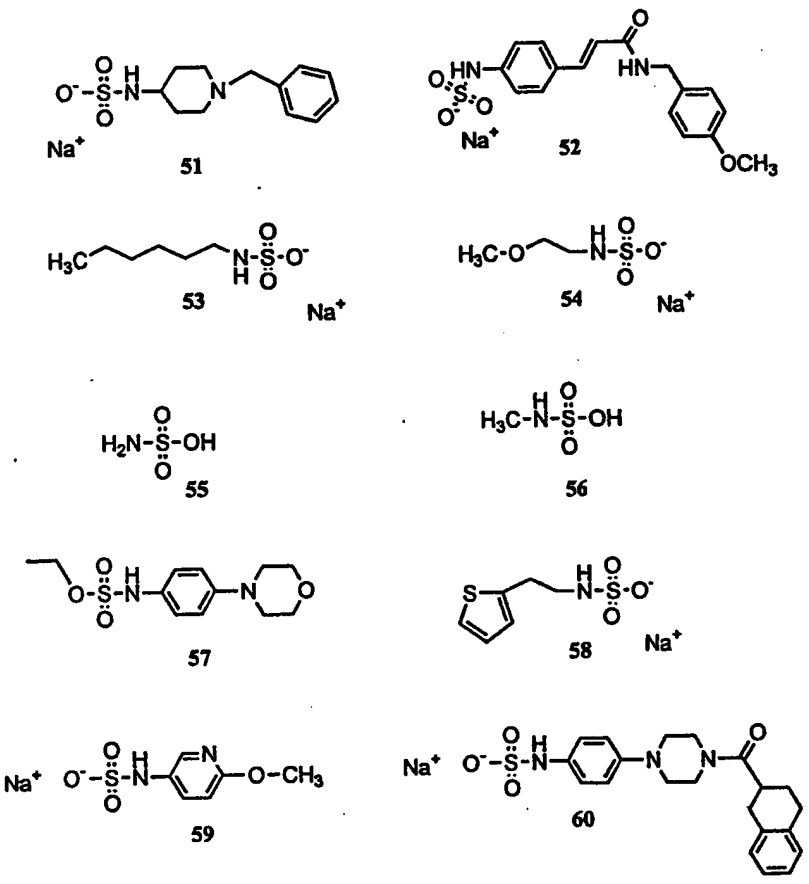


Figure 6

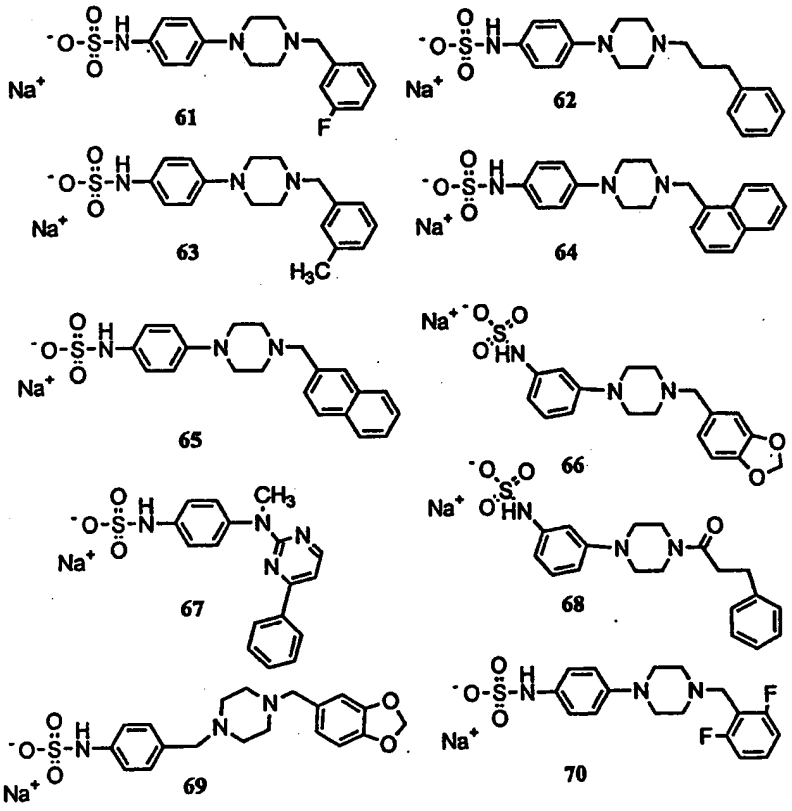


Figure 7

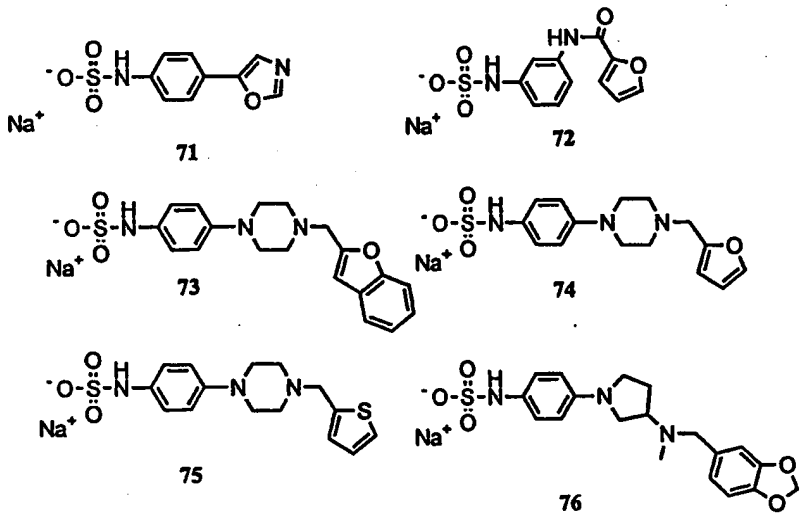


Figure 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/09750

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/165, 31/495, 31/496, 31/5375; C07C 307/110; C07D 295/26, 295/205, 405/10.
US CL : 544/160, 377, 379, 383, 391; 562/37; 514/238.2, 254.1, 254.11, 255.01, 605.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/160, 377, 379, 383, 391; 562/37; 514/238.2, 254.1, 254.11, 255.01, 605.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE STRUCTURE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3,330,775 A (MARQUIS) 11 July 1967, see entire document especially column 2, lines 15-24.	1-4
X	WO 96/26932 A1 (CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED) 06 September 1996, see entire document, especially page 7.	1-3, 7-8
X	DREW et al. Quantitative Structure-Activity Relationship Studies of Sulfamates RNHSO3Na: Distinction between Sweet, Sweet-Bitter, and Bitter Molecules. J. Agric. Food Chem. 11 July 1998, see especially page 3017, Figure 1.	1-2, 4 and 7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
05 June 2003 (05.06.2003)

Date of mailing of the international search report
28 JUL 2003

Name and mailing address of the ISA/US
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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

PCT/US03/09750

Continuation of Box I Reason 2:
The claims relate to an extremely large number of permutations based on the scope of variables as generically set forth in the claims which are not all adequately supported in the description within the meaning of PCT Article 6. The claims have been searched based on the structural makeup of the species recited in claims 3-6.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/09750

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 1,2 (both in part),3-6,7-8 (both in part)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.